SOME CHEMISTRY OF REACTIVE SPECIES FORMED ON OXIDATION OF HYDROXAMIC ACIDS

by

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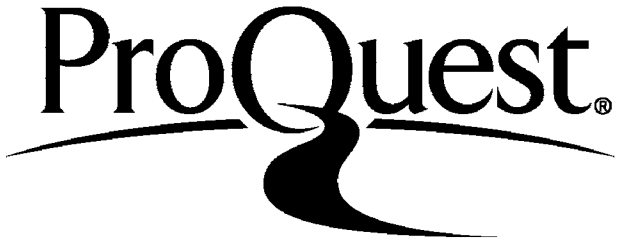

To my family,

ACKNOWLEDGEMENT

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Abstract

Primary and secondary acyl nitroxides [$RCON(O^{\bullet})CHR^1R^2$; R^1 = H, R^2 = alkyl and R^1, R^2 = alkyl] undergo β-H disproportionation to give acyl nitrones [$RCON^+(O^-)=CR^1R^2$] and hydroxamic acids. The acyl nitrones are transient intermediates which have been investigated in this thesis by attempted trapping experiments and by semi-empirical molecular orbital calculations.

The known cycloadduct of 1-adamantanecarbonyl nitrone [$AdCON^+(O^-)=CH_2$] and N-phenylmaleimide has been re-investigated and the pivaloyl analogue obtained. Solution pyrolysis of the former does not appear to regenerate the nitrone. Two N-allyl-hydroxamic acids have been prepared, but one-electron oxidation of these gave no evidence for intramolecular trapping of the double bond.

Synthesis of N-(primary)alkylhydroxamic acids was achieved in this work by benzoyloxylation (benzoyl peroxide) of the n-alkylamine and modification of the usual reaction conditions to stabilize the N-alkyl-O-benzoylhydroxylamine as the hydrochloride; this circumvents acyl transfer to form amide. The results of a kinetic investigation, using e.s.r., of the second-order decay of the corresponding acyl primary-alkyl nitroxides could not be rationalized solely in terms of the strengths of the β-CH bonds.

E.s.r. spectroscopy was also used to study the structure of a stable aroyl t-butyl nitroxide dissolved in a glassy toluene

matrix.

The M.O. calculations compared the reaction co-ordinates for cycloadditions of acyl nitrones to alkenes with those for similar cycloadditions of simple nitrones. As expected, the activation barriers were lower for the acyl nitrones. This investigation led to a comparison of MNDO and AM1 methods of calculation. The former seriously over-emphasises core-core repulsions near the transition state. This is clearly demonstrated by a difference map of energy surfaces obtained by the two methods.

The stilbene derivative, N-t-butyl-O-β-styrylbenzohydroxamic acid has been prepared in order to compare the rate of intramolecular addition of the derived nitroxide to the stilbene double bond with the rate of intermolecular addition of a model nitroxide to trans-stilbene. The results of the kinetic measurements gave an effective molarity of ca. 5×10^5 M, in marked contrast to values of only ca. 1-100 M for intramolecular hydrogen abstraction by acyl nitroxides.

CONTENTS

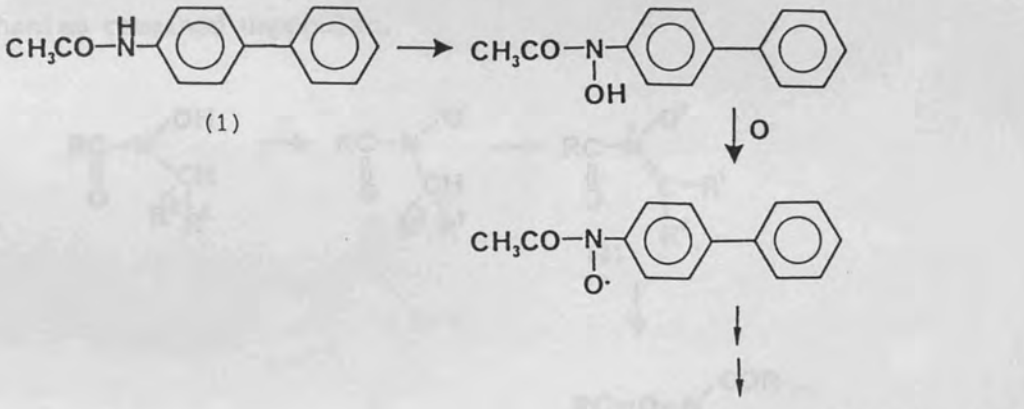
Chapter 1

Introduction

(1) Background

Oxidation at nitrogen is a major process in the metabolism of nitrogen containing compounds. This oxidation results in the formation of N-hydroxyl compounds; the derived N-hydroxyl compounds have a wide range of biological activity.[1]

N-Hydroxylation of amides gives hydroxamic acids. Some of the products resulting from this reaction are toxic to the body, for example, the N-hydroxylation of 4-acet amidobiphenyl (1).[2]



One electron chemical oxidation of hydroxamic acids has aroused much attention since Boyland and Nery postulated that many oxidants can convert hydroxamic acids into acylation agents.[3] This type of acylation may be of biological significance in connection with carcinogenicity of urethane and many aromatic amines, which can be oxidized in vivo to organic hydroxylamines.[4]

With each of the oxidizing agents, acyl nitroxides are

formed as initial products of one-electron oxidation of N-alkylhydroxamic acids. Although free radicals have been detected and characterized in these oxidations, the nature of the acylating agent had remained uncertain until recently; both ionic and free-radical acylation pathways had been proposed.[3,5] N,O-Diacyl-N-alkylhydroxylamines have been suggested by Forrester et al[6] and Waters et al[7] to be the active acylating agents, as well as the main products. Exner in 1956 proposed a mechanism which involved the "N-acyl oxime" (N-acyl nitrone) species as the potent acylating agent,[8] when N-alkylhydroxamic acids are oxidized, but such a mechanism remained unpopular.

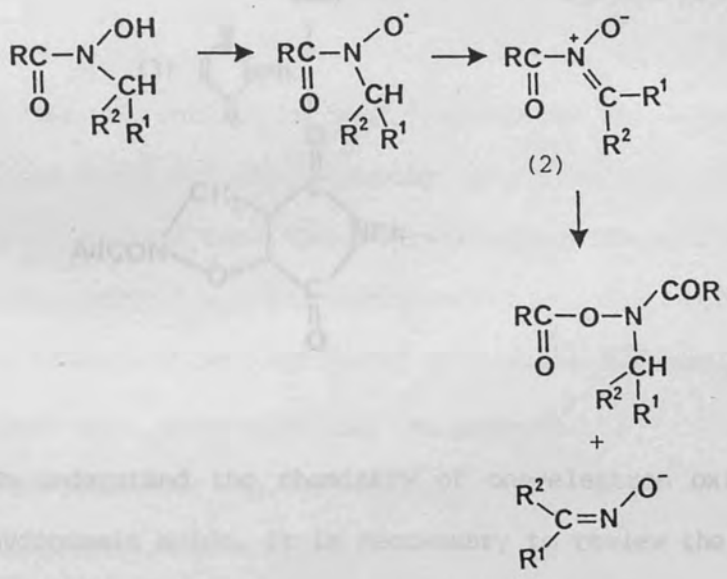


Fig. 1

In recent years a more general mechanism (Fig. 1) has been proposed in which Exner's acyl nitrone (2) is a key intermediate; evidence for the existence of such species includes the trapping

of (2) by 1,3 dipolar cycloaddition to N-phenylmaleimide (Fig. 2) by Perkins et al.[9] However only one case was reported; in which the nitrone was unsubstituted at carbon and the reactivity of the carbonyl group was reduced by the presence of a tertiary alkyl substituent (1-adamantyl; Fig. 2). Work presented in this thesis supports the general mechanism involving the acyl nitrone.

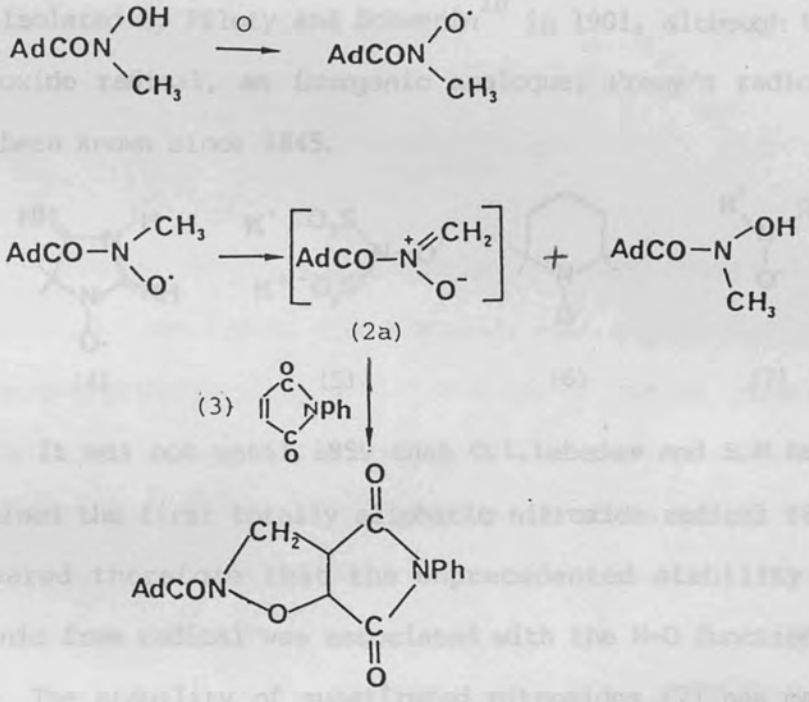


Fig. 2

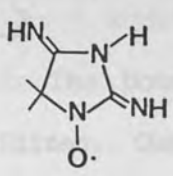
To understand the chemistry of one-electron oxidation of N-alkylhydroxamic acids, it is neccessary to review the chemistry of the initially formed acyl nitroxide radical and its parent function:- the nitroxide radical.

Nitroxide free radicals

Organic free radicals are, by definition, compounds which contain one (or more) unpaired electron(s) and their chemistry is

almost entirely governed by the direct involvement of these electrons. The reactivity and hence the stability depends both on the structure of the radical and physicochemical environment.

Radicals containing the N-O$^{\bullet}$ group, in which the unpaired electron is formally located on oxygen are known as nitroxides. The first organic nitroxide, namely, porhyrexide (4) was prepared and isolated by Piloty and Schwerin[10] in 1901, although the first nitroxide radical, an inorganic analogue; Fremy's radical (5)[11] has been known since 1845.



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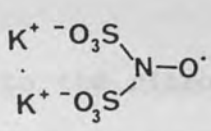

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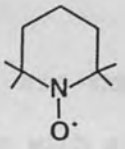

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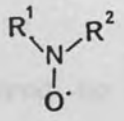


(7)

It was not until 1959 that O.L.Lebedev and S.N.Kazamorski obtained the first totally aliphatic nitroxide radical (6).[12] It appeared therefore that the unprecedented stability of such organic free radical was associated with the N-O function.

The stability of substituted nitroxides (7) has made their application to spin-labelling techniques[13,14,15] invaluable; invariably nitroxides employed as spin labels or probes are di-t-alkyl nitroxides. The chemistry of nitroxide radicals has been extensively reviewed.[16,17,18]

Nitroxide structure

Nitroxides of the general formula (7) are essentially quadrivalent compounds of nitrogen. The bonding in the N-O$^{\bullet}$

function can be described by reference to a partial molecular orbital diagram shown in Fig. 3.

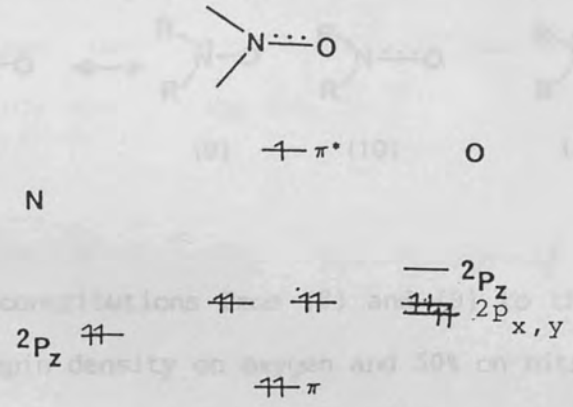


Fig. 3

The bonds to the nitrogen are considered to be sp^2 hybridized. Overlap of these hybrids with a p-orbital (p_x or p_y) on oxygen produces a σ-bond. Overlap of the $2p_z$ atomic orbital of nitrogen or oxygen produces π and π^* bonding and anti-bonding orbitals (Fig. 4) respectively. Two electrons occupy the π-bonding orbital, and the unpaired electron occupies the π^* anti-bonding orbital. This description accounts for a nett bonding effect between nitrogen and oxygen in terms of a 2-centre 3-electron bond.

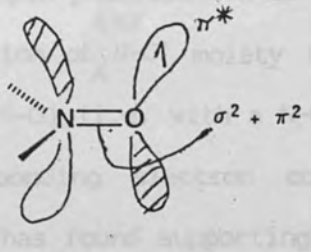
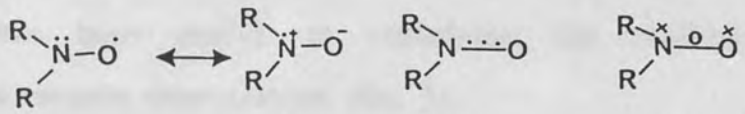


Fig. 4

Nitroxides may be represented in three different ways; as a resonance hybrid of the two extreme structures (8) and (9),[19] by a structure with 3-electron bond (10),[20] or using an alternative

structure based upon Linnett's double quartet hypothesis (11).[21,22]

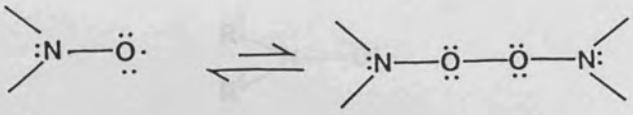


(8) (9) (10) (11)

Equal contributions from (8) and (9) to the hybrid would suggest 50% spin density on oxygen and 50% on nitrogen. This is in fact consistent with studies by H.G. Aurich et al[23,24] in which spin densities on oxygen atom using ^{17}O labelled dialkyl, diaryl and aralkyl nitroxides show spin densities (ρ) on oxygen to be remarkably constant 0.50-0.55. E.s.r studies on phosphorus-containing aryl tert-butyl nitroxides[25] indicate that p_{π}-d_{π} overlap has a negligible effect on spin polarization, whereas the extent of delocalization of the unpaired electron in N-substituted triethylsiloxy nitroxides[26] decreases in the order 4-pyridyl < 2-pyridyl< 3-pyridyl< phenyl, this showing the effect of α-substitution on spin polarization of nitroxides.

The representation of the N-O· moiety in (10), as a structure with five electrons (N-O) (i.e. with a N-O σ-bond and a π-system in which the anti-bonding electron counteracts one of the π-bonding electrons) has found supporting evidence from spectroscopic measurements.[18b] For example, the NO bond length is reported to lie between those of a double bond (1.22 A) and a single bond (1.43 A).

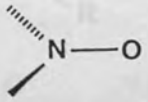
The last model (11), is based on the double quartet hypothesis proposed by Linnett.[21,22] This representation takes into account the mutual orientation of the electron spins. This concept has been useful in explaining the resistance of nitroxides towards dimerization (Eq. 1).



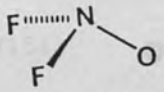
Eq. 1

Dimerization of nitroxide radicals occurs only in special cases e.g. Fremy's radical or at very low temperatures where physically bonded dimers have been detected.

The above structural representations imply that the nitrogen centre is planar: low $^{a}_{N}$ values from e.s.r. studies of alkyl nitroxides (12)[27] strongly suggest that they are nearly planar. By comparison, difluoronitroxide (13)[28] with $^{a}_{N}$ = 94.3 G $^{a}_{F}$ = 142.2 G is considered to be considerably bent. However it



(12)

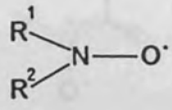


(13)

is clear that in many nitroxides the energy required for quite substantial pyramidal distorsion is small.[29] Semi-empirical and ab initio M.O. calculations are consistent with these observations.[30]

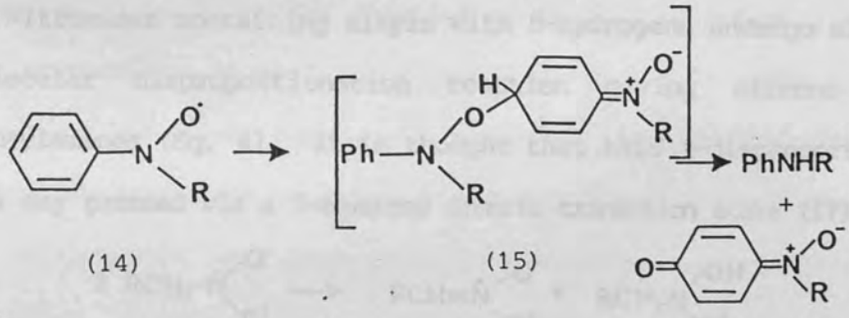
Reactions

The stability of nitroxide radicals, as explain earlier, is due to the inherent stability of the NO• function. Dialkyl nitroxides of the general formula (7), in which R^1, R^2 = t-alkyl groups are very persistent radicals, but when R^1 or R^2 possess an



(7)

α-H the stability is reduced. Many diaryl and aryl t-alkyl nitroxides (14) are also sufficiently persistent to isolate, but when present in high concentration they may decay slowly by a bimolecular process[31] (Eq. 2) in which a nitroxide radical couples to the aryl moiety of a second radical. The dimer, (15), then fragments to non-radical products. In contrast to this slow

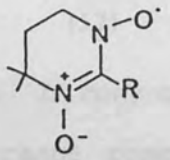


(14) (15)

Eq. 2

bimolecular process, O-C (β) coupling seems particularly rapid in vinyl nitroxides.[32] For these, authentic e.s.r. detection has proved difficult, except where steric interaction or stabilization of the vinyl substituent by conjugation inhibits reaction. For example, it is reported that lifetimes of 1,3-nitronyl

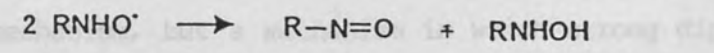
nitroxides (16) are increased relatively to those of simple α-substituted nitroxide;[33] this stabilization is due to conjugation between nitrone-nitroxide group, which results in spin densities on both nitrogens being almost the same.



R=H,Me

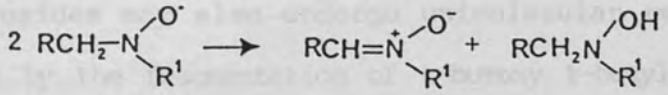
(16)

When nitroxides are mono-substituted (i.e. R^1 = H, R^2 = alkyl) they rapidly disproportionate to nitroso compounds and hydroxylamines (Eq. 3).



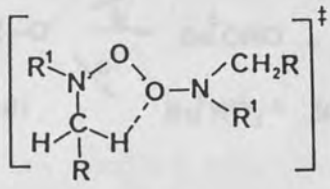
Eq. 3

Nitroxides containing alkyls with β-hydrogens undergo slower bimolecular disproportionation reaction giving nitrone and hydroxylamines (Eq. 4). It is thought that this β-disproportionation may proceed via a 5-membered dimeric transition state (17)



Eq. 4

as proposed by K.U. Ingold et al;[34,35] a transition state related to that for the decomposition of alkylperoxyl radicals by the Russell Mechanism.[36] The measured rate constants lie in the range 10^{-3}-10^{2} $M^{-1}s^{-1}$, although the activation energies range

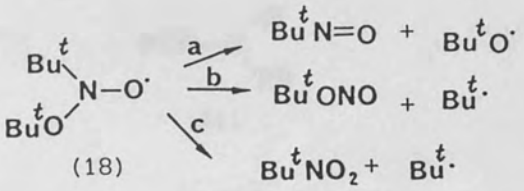


(17)

between 0.6-9.4 kcal/mole. In many cases, therefore, the activation energy is in the range commonly found for diffusion-controlled reactions. The slow rate constants are explained by low Arrhenius pre-exponential factors A, usually ca. 10^4 $M^{-1}s^{-1}$. The measured A factors are substantially lower than those associated with normal radical-radical reactions ca. 10^8-10^{10} $M^{-1}s^{-1}$. This indicates that the reaction does not proceed via a simple mechanism, but a mechanism in which strong dipole-dipole induced orientation effect within a caged radical pair disfavours the self-disproportionation reaction of dialkyl nitroxides.

Evidence for "dimer" formation of dialkyl nitroxides at low temperature has been obtained,[34] with ΔH for dimer formation being of the magnitude expected for dipole-dipole interactions.[35]

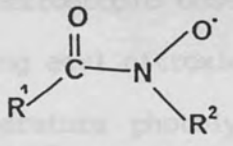
Nitroxides may also undergo unimolecular reaction as exemplified by the fragmentation of t-butoxy t-butyl nitroxide (18).[37] Such species are short-lived, fragmenting by three known pathways (a, b, c). The principal pathway is found to involve path (b), that is t-butyl nitrite is formed as has been previously suggested by A. Mackor et al.[38] Path (a) is, in fact, much faster but reversible in the presence of excess $Bu^tN{=}O$.



(18)

Acyl nitroxides

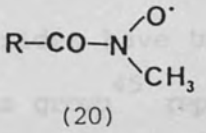
Nitroxides of the general formula (19), where an acyl group is attached to the nitroxide nitrogen, are known as acyl nitroxides. The acyl group affects the structure and reactivity and pattern of reaction of these radicals.



(19)

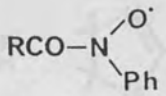
History

Acyl nitroxides of general formula (20) were first detected by Gutch and Waters[39] in an e.s.r. study of fast flow oxidation of primary hydroxamic acids and N-hydroxycarbamates in aqueous solution.



(20)

Aurich and Baer observed acyl nitroxides[39b] (21: R = CH_3, Ph etc) by e.s.r. during oxidation of N-phenylhydroxamic acids using nickel peroxide. It was noted that low ^aN values (^aN = 7-8 G)

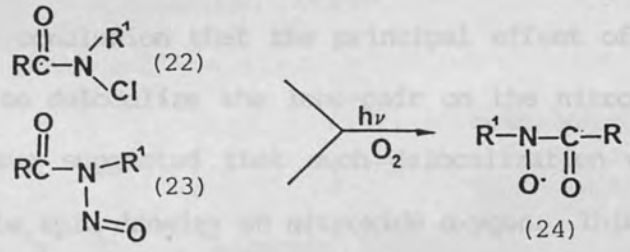


(21)

resulted relative to the dialkyl and diaryl nitroxides, which showed typically higher ^{a}N values of 15-17 and 9-11 G respectively. This can be explained by contributions from resonance structures (see later) which result in the removal of spin density from the nitroxide nitrogen.

Synthesis

Since initial spectroscopic observation, many methods have been found for generating acyl nitroxides for e.s.r. observation. For example, low temperature photolyses of N-chloro (22) and N-nitroso-N-alkylamides (23) in the presence of O_2 gave the corresponding acyl nitroxides (24).[40,41]



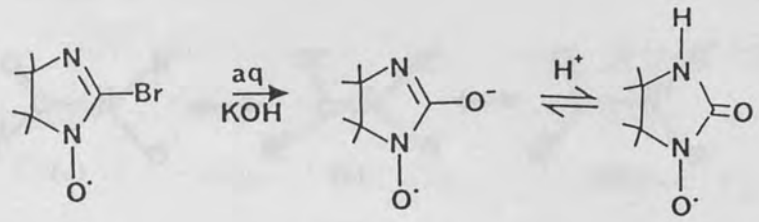
(22)

(23)

(24)

Cyclic acyl nitroxides have been investigated by many groups.[42,43,44] Ullman's group[45] reported the formation of an unisolated cyclic carbamoyl nitroxide upon hydrolysis of 2-bromo-4,4,5,5-tetramethyl-imidazolin-1-oxyl (25) with aqueous KOH directly in the cavity of an e.s.r. spectrometer.

Although these radicals were unambiguously observed and

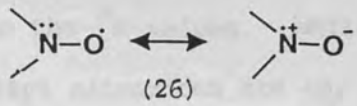


(25)

low ^{a}N values reported, it was not until 1973 that Perkins and Ward isolated several acyl t-butyl nitroxides.[46]

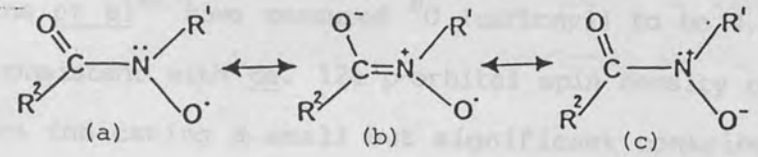
Structure

Dialkyl nitroxides are considered to have about 50% spin density on oxygen (26). The acyl nitroxides contain somewhat



(26)

greater spin density on oxygen and the calculated OH-bond strength involved in the corresponding hydroxamic acids are greater than those present in hydroxylamines. This observation led to the conclusion that the principal effect of acyl conjugation was to delocalize the lone-pair on the nitrogen. Perkins et al[47] have suggested that such delocalization would tend to localize the spin density on nitroxide oxygen. This is expressed by hybrid structure (27b). The electron delocalization represented by (27b) is analogous to that in amides. If it is important, spin must be more localized on oxygen than in dialkyl nitroxides. Supportive evidence for the distribution of spin densities is provided by e.s.r..[47] The distribution of π-spin densities (ρ) in the NO bond is related to the nuclear hyperfine



(a) (b) (c)

(27)

coupling constants (^{a}N and ^{a}O)[48] Eq. 5. The greater the spin

$$^{a}N = Q^{N}_{NN}\ \rho_{N}^{\pi} + Q^{N}_{CO}\ \rho_{O}^{\pi}$$

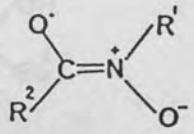
$$^{a}O = Q^{O}_{CO}\ \rho_{O}^{\pi} + Q^{O}_{NN}\ \rho_{N}^{\pi}$$

Eq. 5

density, the greater the ^{a}X values. Whilst ^{a}N values normally associated with dialkyl nitroxides are ca. 15-17 G, much smaller values are shown by acyl nitroxides (ca. 7-8 G) consistent with reduced spin density on nitrogen.

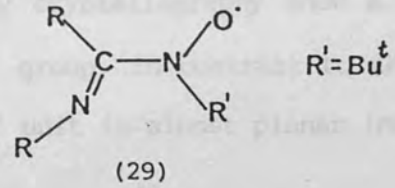
σ—π interactions(Q) parameters for ^{14}N and ^{17}O can be obtained by a correlation between isotropic hyperfine coupling constants (hfs) and the electron-nuclear dipolar splitting (Ti, i = ^{14}N, ^{17}O) as determined from combined measurement of isotropic and anisotropic hfs.[48] Thus hyperfine coupling constants ^{a}N, ^{a}O are directly related to ρ_{N}, ρ_{O} respectively (this neglects any contributions to splitting from spin densities on adjacent atoms which are usually small). Aurich et al, using ^{17}O labelled nitroxides,[23,24] have found a very good correlation between ^{a}N and ^{a}O. This picture is however an oversimplification of the π-electron distribution in acyl nitroxides. For

benzoyl t-butyl nitroxide where ^{a}N = 7.75 G and ^{a}O = 20.3 G Jenkins et al[49] have measured ^{a}O (carbonyl) to be 4.4 G. This was consistent with ca. 12% p-orbital spin density on carbonyl oxygen indicating a small but significant contribution from structure (28).


(28)

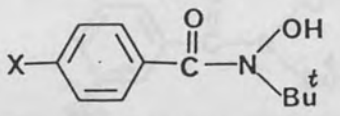
The interpretation of ^{a}O (carbonyl) is complicated by the results of INDO calculations which suggests that ρO (carbonyl) may be offset by a negative spin density (-4%) on carbon. INDO calculations were made assuming coplanar HCONHO· with oxygen atoms anti-related; recent MNDO calculations[50] of p-orbital spin density are consistent with the INDO calculations.

A similar spin polarization effect, giving negative spin density on the imino-carbon of α-imino alkyl nitroxides (29), has also been discussed.[23]


(29)

The role of the lone-pair delocalization seems to be supported by an excellent correlation between the OH-bond strength of benzohydroxamic acids (30) and Brown's σ^{+} constants[51] [the greater the lone-pair delocalization from nitrogen in the

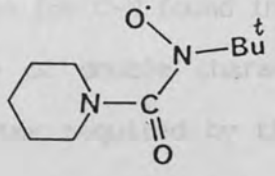
radical, the greater the spin density located on oxygen in the radical and the greater the O-H bond strength in the hydroxamic acid].



(30)

	B.D.E (OH)
a: X=H	77.2
b: X=Ph	76.7
c: X=NO_2	79.4
d: X=OMe	75.1

Although the change in ^{a}N was small with the variation of substituent, there is a good correlation between ^{a}N and σ^{+} over the range p-NO_2 - p-$N(Me)_2$ including eight p-substituted aroyl nitroxides.[47] These results show that conjugation of carbonyl across the benzene ring competes with amide delocalization of the nitrogen lone pair. This effect is magnified by the removal of the benzene ring and direct attachment of the substiuent to the carbonyl group e.g. t-butyl dialkyl amino carbonyl (31). Such a radical has much of the character of an dialkyl nitroxide with ^{a}N = 15-17 G. X-Ray crystallography show a torsional angle of 117^{o} in the O-C-N-O$^{\cdot}$ group, in contrast to the aroyl nitroxides in which the O=C-N-O$^{\cdot}$ unit is almost planar (next section).

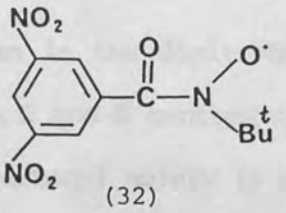


(31)

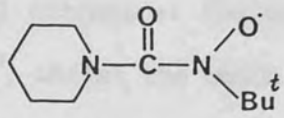
Geometry

X-Ray crystallographic studies on two acyl nitroxides

(32), (33) have been reported by M.J. Perkins et al.[52] The results have provided a valuable insight into the structures of these acyl nitroxides.

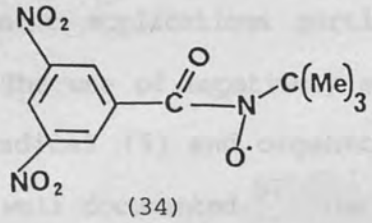


(32)



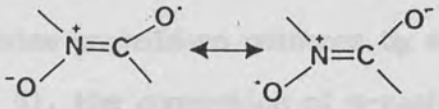
(33)

X-Ray crystallography on t-butyl-3,5-dinitrobenzoyl nitroxide (32) (a green solid, mpt. 100°C) showed a structure in which the CO-NO• moiety is essentially planar: the dihedral angle between these two groups was about 14°. The carbonyl-oxygen and nitroxide-oxygen assume an "anti" relationship (34)[53] and the NO• bond length (1.28 A) lies within the range normally associated with nitroxides. The intermediacy of the C-N bond length



(34)

(1.38 A) between those for C-N found in amides and C-N, suggested a substantial degree of double character; consistent with the double bonded character required by the resonance hybrids (27b) and (28); that is there is marked delocalization in the CO-N(O•)-moiety of (34). In the case of the structure piperidinocarbonyl nitroxide (31) the carbonyl nitroxide C-N bond length is much

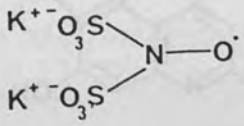


(27b) (28)

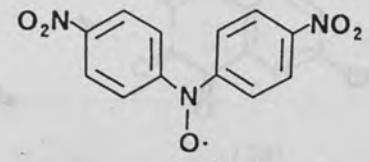
greater than in the dinitrobenzoyl nitroxide: the torsion angle between the C and N centres is 56^{o}, whilst the amide unit of the piperidinocarbonyl moiety is essentially planar. Furthermore, in the crystal the nitroxide nitrogen is pyramidalized, with the oxygen atom ca. 12^{o} out of the CNC plane. Competing interactions between the carbonyl group and the two nitrogen atoms results in less nitroxide delocalization in (31) than in (32).

Reactions of acyl nitroxides

The increased spin density at nitroxide oxygen in acyl nitroxides compared with dialkyl nitroxides leads to increased reactivity. The benefits of this increased reactivity have been exploited in synthetic applications particularly as homolytic oxidants.[54,55,56] The use of negatively substituted nitroxides such as Fremy's radical (5) and organic nitroxides (35) as oxidants have been well documented.[57] The former has been used



(5)



(35)

extensively as an oxidizing agent in the conversion of monohydric phenols to quinones. It is reported that acyl t-butyl nitroxides

can be used as homolytic oxidizing agents and like Fremy's radical, they oxidize phenols to quinones by a similar mechanism. For example (Fig. 5), the conversion of α-naphthol (36) to the

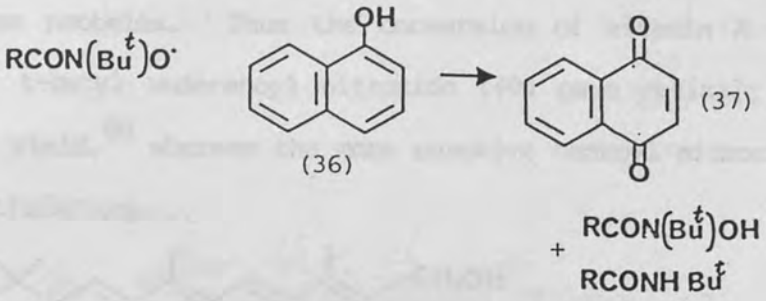
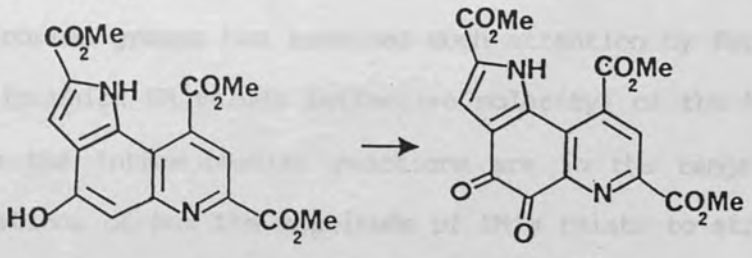


Fig. 5

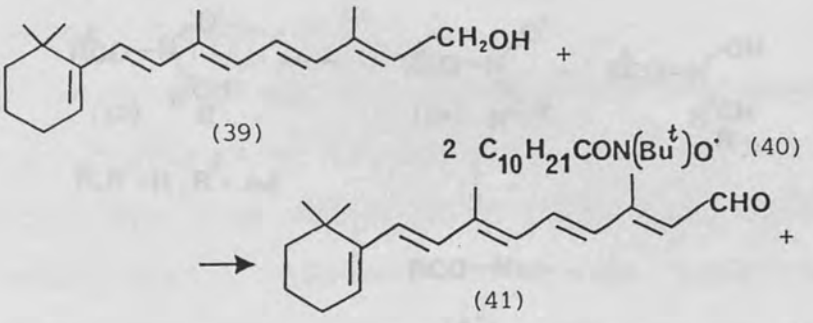
corresponding quinone (37).[58] In most cases of conversion of phenol to quinone the yields are very good, although no p-benzoquinone was obtained from phenol. Since these reaction are effected in organic solvents, the acyl nitroxide has advantages over Fremy's radical which is inapplicable in organic solvent without the aid of a phase transfer agent. The application of acyl nitroxide oxidation in the synthesis of natural products, for example, the microbial co-enzyme methoxatin (38),[59] has shown their versatility.



(38)

Another potential value, is the efficient and selective oxidation of allylic and benzylic alcohols to the corresponding aldehydes or ketones. This is primarily due to α-CH bonds

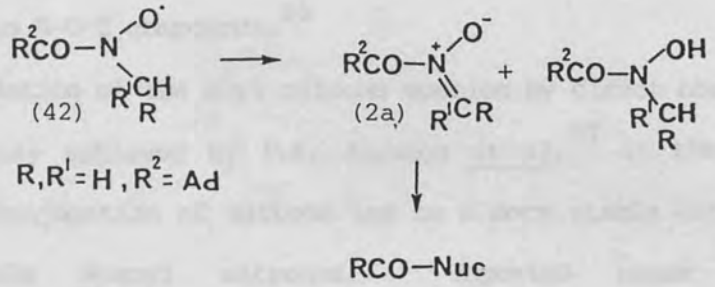
being weaker than those in saturated alcohols allowing oxidative selectivity. Various acyl nitroxides can be used which exemplify the possibilty of tailoring the reagent to solve particular oxidation probelms. Thus the conversion of vitamin A alcohol (39) by t-butyl undecanoyl nitroxide (40) gave retinal (41) in ca. 90% yield,[60] whereas the more reactive benzoyl nitroxide was less satisfactory.



Acyl t-alkyl nitroxide have proven good systems for investigating aspects of radical reactivities due to their ease of formation, coupled with their high reactivity. Comparison of inter- and intramolecular hydrogen abstraction reactions using acyl nitroxide groups has received much attention by Perkins et al[61,62] in which EM values (effective molarity) of the hydrogen donors in the intramolecular reactions are in the range 1-100. Investigations of how the magnitude of EM's relate to structural geometry of radicals was considered, and how this relates to the much higher EM values encountered in many ionic intramolecular reactions.

Acyl nitroxides [$RCONC(O^{\cdot})R^{1}$] in which R^{1} = H or

R^1 = primary, and secondary alkyl, undergo disproportionation[63,64] as found in alkyl nitroxide radicals (see alkyl nitroxide sub-section). In the case of acyl alkyl nitroxides (42), this disproportionation leads to acyl nitrones (2a), which are not isolated, but acylated by nucleophiles inter alia to give new product (43); the reactivity of the N-acyl nitrone does not allow its isolation.

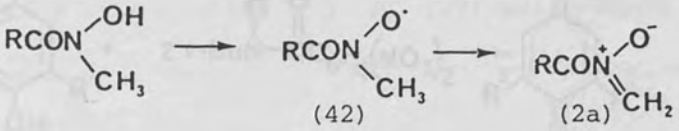


(43)

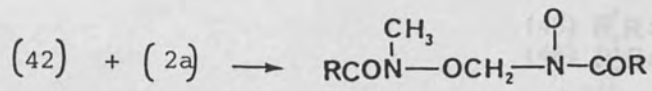
Hussain et al[65] has shown that by structural modification it is possible to trap the acyl nitrone (Fig. 2) by cycloaddition. Nucleophilic attack on carbonyl can be reduced by sterically hindering substitution by a bulky tertiary alkyl group R^2 = 1-Ad and R, R^1 = H, the reactivity of the nitrone maximized by removing substituents. Thus with (2a) and N-phenylmaleimide the cycloaddition product was formed in 70% yield. In this thesis other examples of interception of acyl nitrone are to be studied using other bulky R groups.

Further evidence for the existence of a simple acyl nitrone involves the existence of a nitrone-nitroxide spin adduct (44), formed by the reversible trapping of an acyl nitroxide by the nitrone,[63] in which conformation about the NO bond in the addend moiety has been studied. The calculated $\Delta G^{\neq}$ for rotation

about N-O is ca. 8 kcal/mole, this being similar to the N-O bond



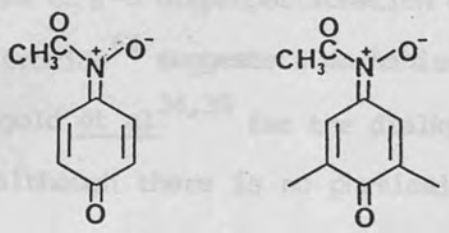
(42) (2a)



R= Ad (44)

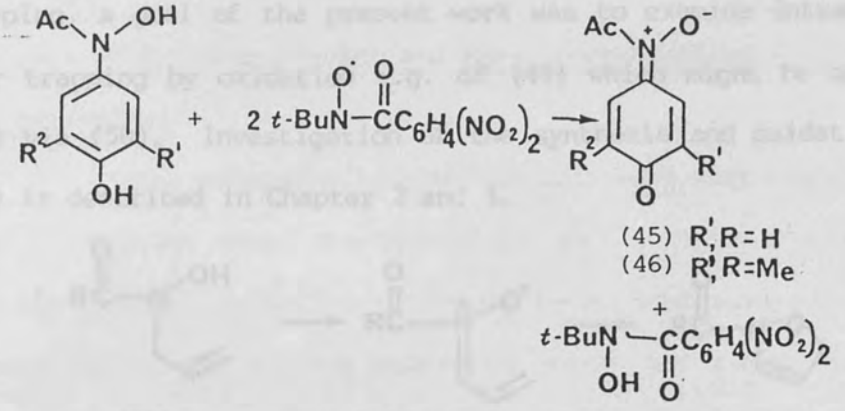
rotation in N-O-C compounds.[66]

Validation of the acyl nitrone species by direct observation was recently achieved by P.F. Alewood et al;[67] in their work, extended conjugation of nitrone led to a more stable entity than the simple N-acyl nitrones. Reported cases include N-acetyl-1,4-benzoquinone-imine-N-oxide (45) and its dimethyl analogue (46).

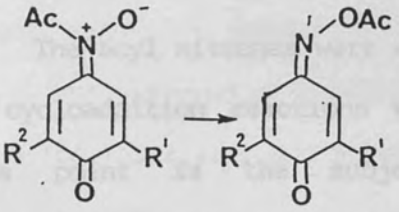


(45) (46)

The acyl nitrone (45) appears to be indefinitely stable at -75°C whereas the acyl nitrone (46) is reported to be stable up to -15° C; elucidation of these structure was by NMR spectroscopy and product studies. Above the stable temperature the acyl nitrone underwent what was said to be an intramolecular rearrangement to N-acetoxyl-1,4-benzoquinone imines (47). The mechanism of rearrangement is unknown.



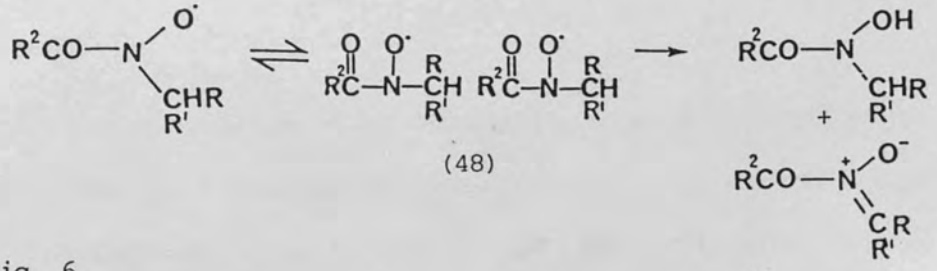
(45) R', R = H
(46) R', R = Me



(47)

Kinetics of disproportionation

Kinetic studies of β-H disproportionation on N-methyl[63] and N-benzyl benzoyl nitroxide[64] suggests a mechanism similar to that proposed by K.U. Ingold et al[34,35] for the dialkyl nitroxide (see earlier) (Fig. 6) although there is no physical evidence at low temperature for the existence of any dipole-dipole dimer (48). Up to now, information about the structural orientation of acyl nitroxide radicals in the transition state has remained elusive.

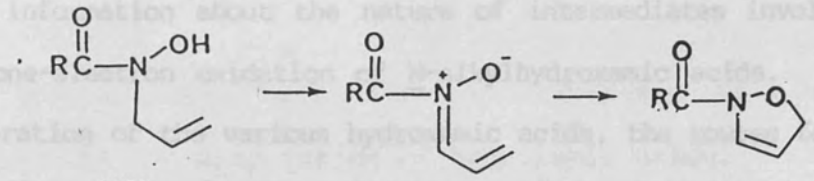


(48)

Fig. 6

In addition to extending our knowledge of intermolecular

trapping, a goal of the present work was to examine intramolecular trapping by oxidation e.g. of (49) which might be to give (51) via (50). Investigation of the synthesis and oxidation of (49) is described in Chapter 2 and 3.



(49) (50) (51)

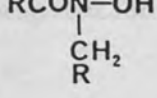
The acyl nitrones were expected to have enhanced reactivity in cycloaddition reactions when compared with other nitrones. This point is the subject of critical examination by semi-empirical M.O. methods in Chapter 5.

Chapter 2

Synthesis of hydroxamic acids and their corresponding acyl nitroxide.

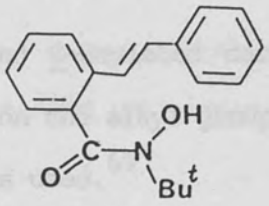
The target molecules involved in this work were designed to give information about the nature of intermediates involved in the one-electron oxidation of N-alkylhydroxamic acids. In the preparation of the various hydroxamic acids, the routes followed were adaptations of well established methods of preparation. The target molecules incorporated steric groups, isolated double bonds, and conjugated double bonds, designed to give information about the reactivity and structure of derived acyl nitroxides and acyl nitrones.

The syntheses can be divided into two sections; (I) The preparation of N-(primary)alkylhydroxamic acids with specific features to enable the effects on the reactivity of the acyl nitroxide to be studied and to facilitate the trapping of the reactive acyl nitrone by intra- or intermolecular interception.



R = CH_2=CH−, R^1 = Ph (49a)
R = CH_2=CH−, R^1 = Ad (49b)
R = H, R^1 = Ad (52a)
R = H, R^1 = Bu^t (52b)
R = Et, R^1 = Ph (53)
R = Ph, R^1 = Ph (54)

(II) The preparation of an N-t-alkylhydroxamic acid (55) with the presence of a conjugated double bond; required to study the intramolecular radical addition of acyl nitroxide radical to double bond (see Chapter 3).



(55)

Preparations

Several general methods have evolved through many years of research in the preparation of hydroxamic acids.[68] The key intermediate involved in most methods is the N-alkylhydroxylamine (56) which can be prepared by two main routes.

R–NHOH

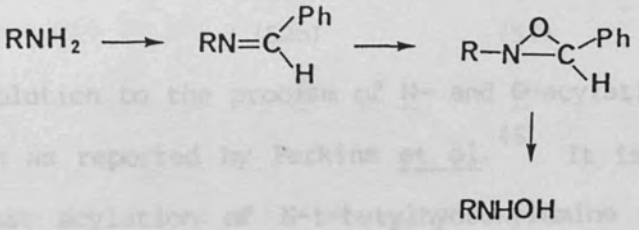
(56)

(I) The preparation of N- 1^{o}, 2^{o}, 3^{o} alkylhydroxylamine by scheme 1 involving the oxidation of amine to hydroxylamine.

$$RNH_2 \longrightarrow RNO_2 \longrightarrow RNHOH$$

Scheme 1

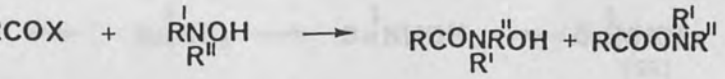
(II) The preparation of N-t-alkylhydroxylamines by scheme 2.



Scheme 2

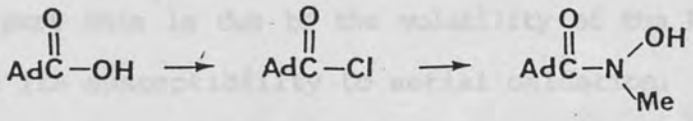
Acylation of the N-alkylhydroxylamines normally gives

mixtures of the N- and O-acylated derivatives (scheme 3), the proportions depending on the alkyl group, the acylating group and the reaction conditions used.[69]



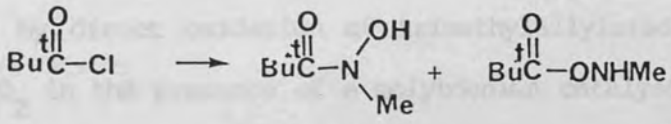
Scheme 3

The synthesis of N-methyl-N-adamantanecarbonylhydroxylamine (52a) in this work has been carried out by this method, in which almost exclusive N-acylation occurs in good yield (66% based upon N-methylhydroxylamine hydrochoride). In contrast, in the synthesis of N-methyl-N-pivaloylhydroxylamine (52b) in this work,



(52a)

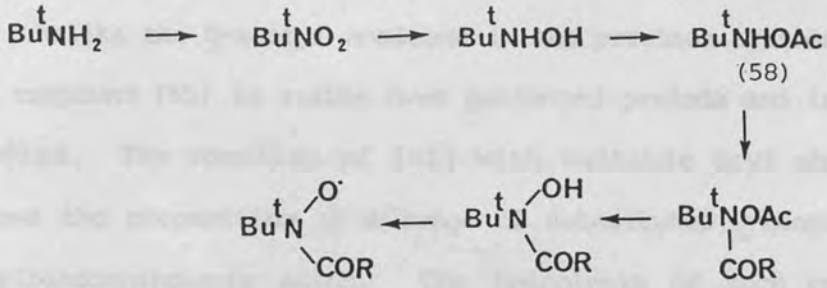
both N- and O-acylation occurs, separation of products (52b) and (57) was by flash chromatography using silica gel, yield 16%.



(52b) (57)

The solution to the problem of N- and O-acylation involves O-protection as reported by Perkins et al.[46] It is found, for example, that acylation of N-t-butylhydroxylamine with acetic anhydride gives essentially pure O-acetyl-N-t-butyl-hydroxylamine (58). This could be acylated on nitrogen to give (59),

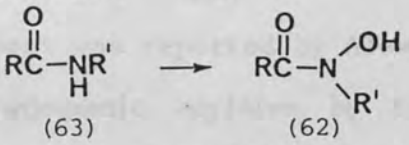
followed by the removal of the acetyl group to give a variety of hydroxamic acids RCON(Bu^t)OH (60) which could be oxidized to give stable isolatable radicals (61) (R = alkyl, aryl, alkoxy, dialkylamino) (see scheme 4). There are several disadvantages



Scheme 4

in this method. Firstly, the method is tedious and the yield obtained in the reduction of Bu^tNO_2 is erratic and frequently poor. In part this is due to the volatility of the hydroxylamines and its susceptibility to aerial oxidation. In some instances the hydrolysis of the O-acyl derivatives (59) requires an inert atmosphere and this conversion to the hydroxamic acid has also presented other difficulties.

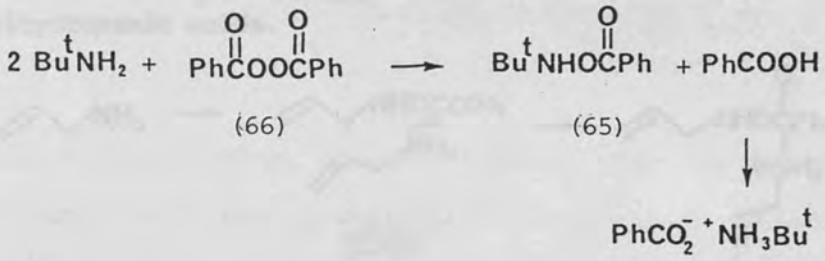
Sammes group[70] has shown that hydroxamic acids (62) can be prepared by direct oxidation of trimethylsilylated amides (63) using H_2O_2 in the presence of a molybdenum catalyst, but yields have been found to be low.



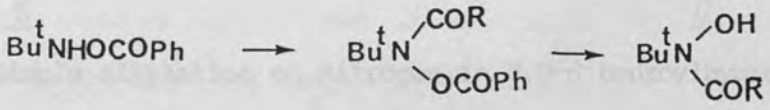
A new procedure was reported by P.F. Alewood et al.[71] This was based upon G. Zinner's[72] one step synthesis of O-benzoyl-N-t-butylhydroxylamine (65) directly from t-butylamine (64). This

method involves a first addition of alkylamine to benzoyl peroxide (66) in benzene over a period of 15-30 mins, followed by a second addition of a similar quantity of amine to the mixture and the temperature of reaction raised to 40°C for 3-4 hours.

Unlike the O-acetyl analogue in the previous synthesis, the key compound (65) is stable over prolonged periods and is easily handled. The reaction of (65) with suitable acyl chlorides allows the preparation of a range of substituted O-benzoyl-N-t-butylbenzohydroxamic acids. The hydrolysis of such compounds (67) with ethanolic barium hydroxide, followed by acidification

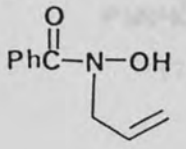


with glacial acetic acid requires an inert atmosphere and could only be achieved in approximately 60-90% yield. A major improve-



(67)

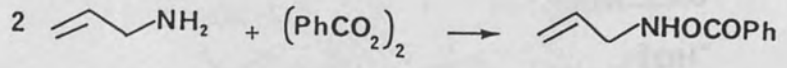
ment in this respect was reported by Alewood *et al*[71] in the deprotection of hydroxamic acylates by transamidation using hydrazine hydrate. Reaction of an ethanolic solution of (67) with large excess (7.5 mole equiv.) of hydrazine hydrate at 40°C



(49a)

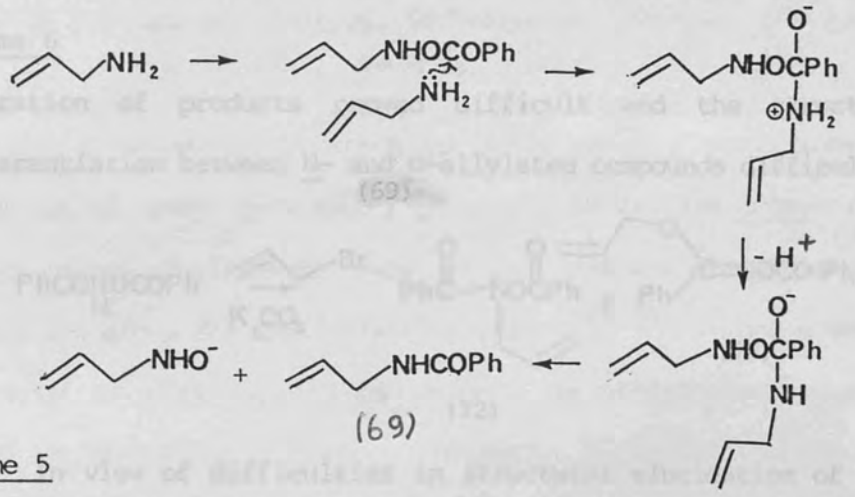
for 1 1/2 hours gave hydroxamic acid (60) of high purity in yields greater than 90%.

In an attempted preparation of N-allylbenzohydroxamic acid (49a) using the Alewood method, the preparation of N-allyl-O-benzoylhydroxylamine (68) proved impossible due to a rearrangement to an amide (69) (as shown by its IR spectrum) [scheme 5] previously reported,[72b] where R = primary alkyl . This prompted



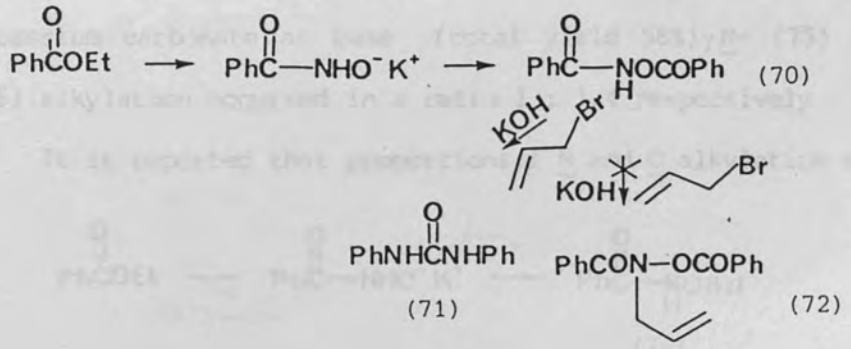
(68)

the investigation of alternative methods for the preparation of N-allylhydroxamic acids.



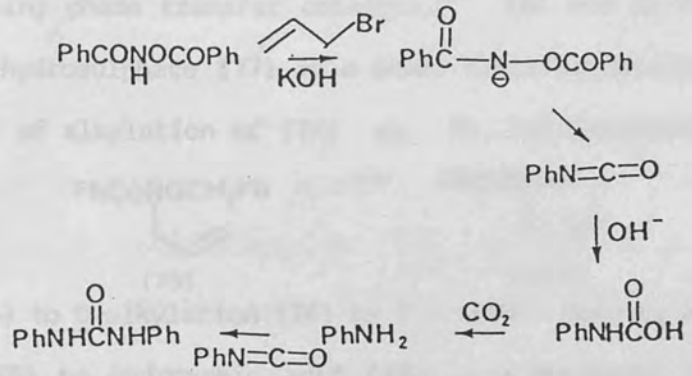
Scheme 5

Simple alkylation on nitrogen in N,O-dibenzoylhydroxylamine (70) was attempted as a route to prepare (71) using KOH as base.



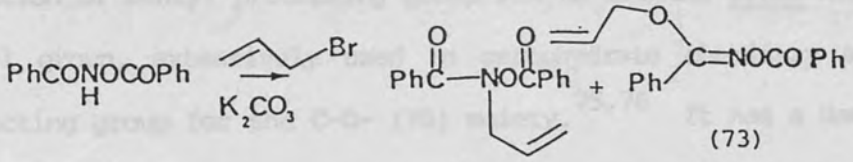
(71) (72)

This reaction, too, could not be realised. Rearranged products (71) resulting from Lossen rearrangement[73] (scheme 6) were formed. When the reaction was carried out using potassium carbonate as base, N- (72), and O- (73) alkylation occurred. The



Scheme 6

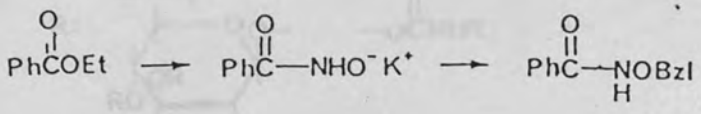
separation of products proved difficult and the structural differentiation between N- and O-allylated compounds difficult.



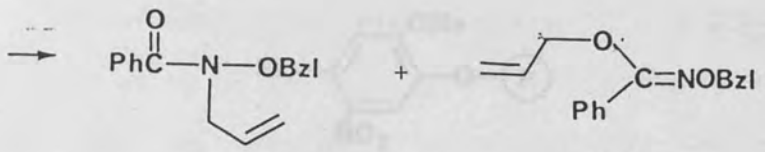
(72) (73)

In view of difficulties in structural elucidation of (71) and (73), the use of a benzyl group as an O-protection group was considered. The alkylation of (74) was carried out using potassium carbonate as base (total yield 58%); N- (75) and O- (76) alkylation occurred in a ratio 1 : 1.4 respectively.

It is reported that proportions of N and O alkylation can be



(74)

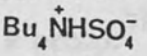


(75) (76)

varied using a phase transfer catalyst.[74] The use of tetrabutylammonium hydrosulphate (77) as a phase transfer catalyst reduced the yield of alkylation of (74) to 9%, but increased the ratio

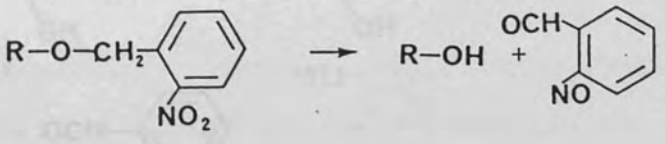
(75) (49a)

of N- (75) to O-alkylation (76) to 1 : 1.05. However attempts to reduce (75) to hydroxamic acid (49a) were abandoned due to the low yield of (75) and difficulties in isolation.

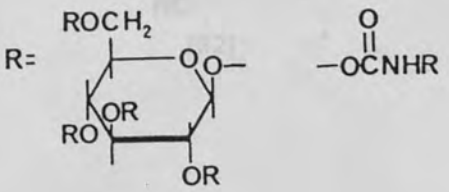


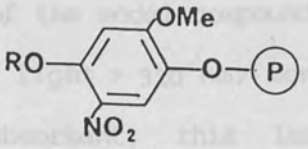
(77)

An alternative approach to the planned electrochemical reduction of benzyl protecting group was to use the ortho-nitrobenzyl group, extensively used in carbohydrate chemistry as a protecting group for the C-O- (78) moiety.[75,76] It has a useful property in that it can be removed by photolysis using UV > 320 nm in various solvents. Recently, separation of products has been improved by the binding of the ortho-nitrobenzyl group to various copolymers (79) such as styrene-divinylbenzene.[77]



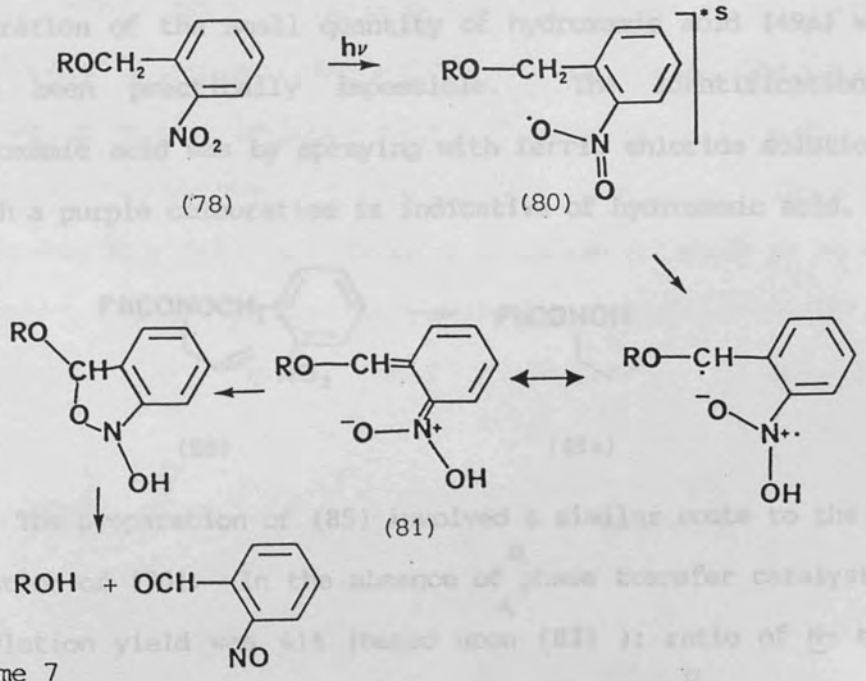
(78)





(79)

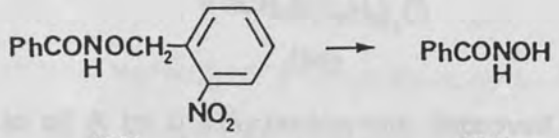
The mechanism involved in photochemical reduction has been studied by Gravel et al.[78] It is thought to involve the photoexcitation of ortho-nitro group (78) to an excited singlet state (80), which abstracts the benzylic hydrogen and leads to the formation of a quinoid species (81), leading to the eventual formation of an alcohol and nitrosocompound (82). Photoexcitation of ortho-nitro groups (scheme 7) to an excited singlet species containing degrees of triplet spin character are known; the degree depending on the R group.[78]



(78) (80) (81) (82)

Scheme 7

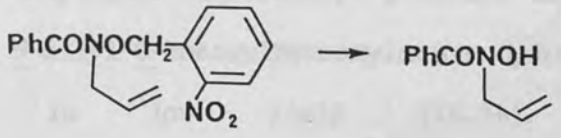
In the case of the model compound (83) in CCl_4, photolysis was done using UV light > 320 nm, monitoring by t.l.c. using silica gel as absorbant; this led to the formation of benzohydroxamic acid (84) identified by comparison with the authentic benzohydroxamic acid. The preparation of N-benzoyl-O--ortho-nitrobenzylhydroxylamine (85) was achieved via a route



(83) (84)

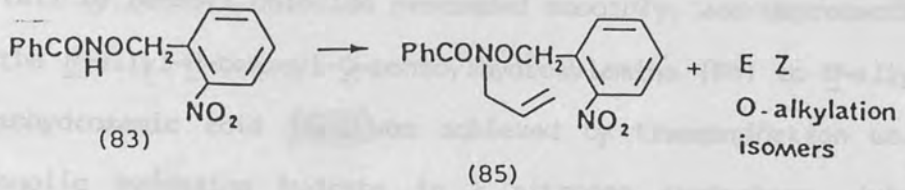
similar to that of N-benzoyl-O-benzylhydroxylamine (74).

In the case of N-allyl-N-benzoyl-O-ortho-nitrobenzylhydroxylamine (85), photolysis led to a complex mixture, (monitored by t.l.c. on silica gel using various solvent systems) in which the separation of the small quantity of hydroxamic acid (49a) would have been practically impossible. The identification of hydroxamic acid was by spraying with ferric chloride solution in which a purple colouration is indicative of hydroxamic acid.



(85) (49a)

The preparation of (85) involved a similar route to the preparation of (75). In the absence of a phase transfer catalyst the alkylation yield was 41% (based upon (83)); ratio of N- to O-alkylation is 2.1 : 1. In the presence of a phase transfer



(83) (85)

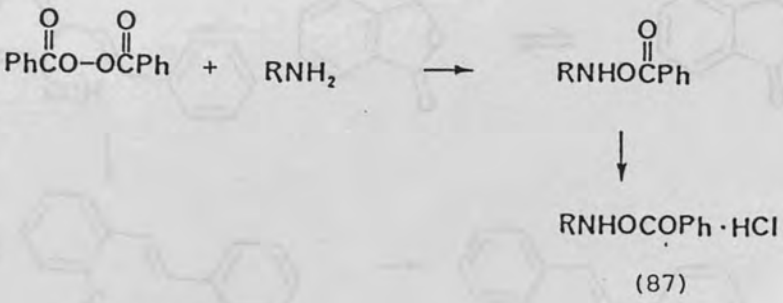
catalyst N-benzyl-N-triethylammonium chloride (86), the alkylation of the nitrobenzylhydroxamate gave a poorer yield (25%),

$$PhCH_2\overset{\oplus}{N}(C_2H_5)_3\overset{\ominus}{Cl}$$

(86)

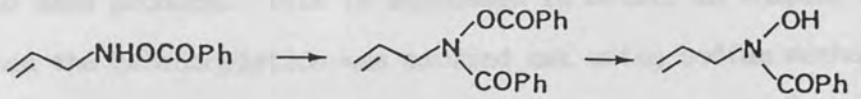
but the ratio of N to O alkylation was improved to 3.9 : 1.

The preparation of N-allylbenzohydroxamic acid (49a) was eventually achieved by referring back to Zinner's method as used in synthesizing primary N-benzyl-O-benzoylhydroxylamine by R.O.C. Norman et al.[79] The rearrangement to amide of N-allyl-O-benzoylhydroxylamine prepared by the Zinner/Alewood procedure was substantially reduced using a deficiency of amine. The resulting hydroxylamine was isolated as the hydrochloride by addition of hydrogen chloride gas. Following this procedure, using approx. equimolar allylamine and benzoyl peroxide followed by hydrogen chloride, N-allyl-O-benzoylhydroxylamine hydrochloride (87) was obtained in low yield (16.5%). N-Acylation



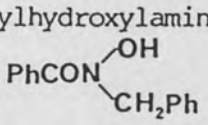
(87)

of (87) by benzoyl chloride proceeded smoothly, and deprotection of the N-allyl-N-benzoyl-O-benzoylhydroxylamine (88) to N-allyl-benzohydroxamic acid (49a) was achieved by transamidation using ethanolic hydrazine hydrate in a nitrogen atmosphere, (yield 37%).

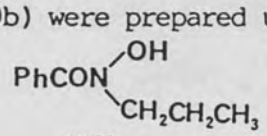


(88) (49a)

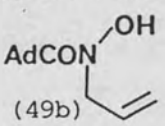
The target molecules N-benzylbenzohydroxamic acid (54), N-n-propylbenzohydroxamic acid (53) and N-allyl-N-(1-adamantane)-carbonylhydroxylamine (49b) were prepared using this method.



(54)

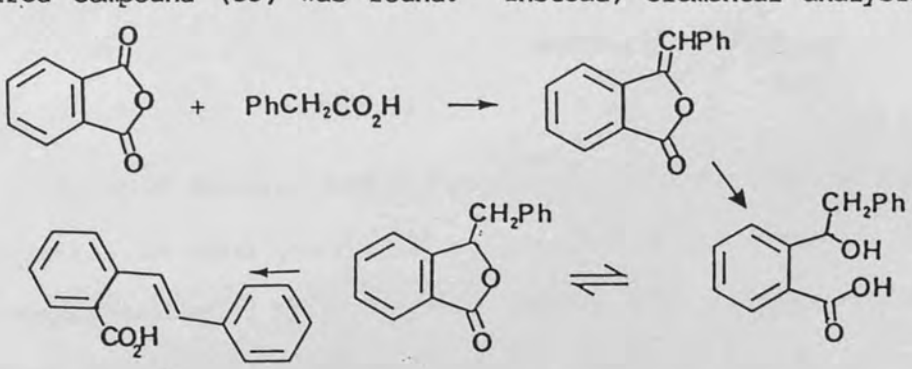


(53)

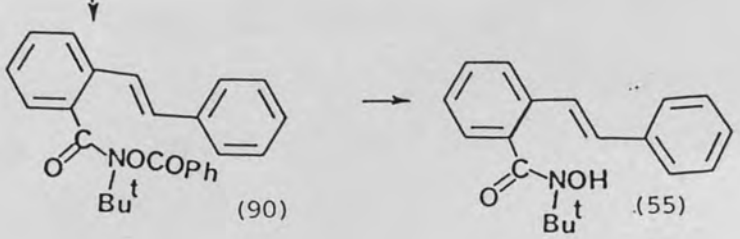


(49b)

A short piece of work involved in this thesis involved the preparation of the stilbenecarbonylhydroxylamine (90) as shown in scheme 8. Deprotection of the O-benzoylhydroxylamine (91) was attempted using ethanolic hydrazine hydrate, but none of the required compound (55) was found. Instead, elemental analysis



Scheme 8



(90) (55)

and spectroscopic study of a crystalline product suggested that oxygen had been incorporated and a hydroperoxide may have been formed. Similarly the attempted deprotection of (55) with ethanolic barium hydroxide followed by the extraction process gave the same product. This is discussed in detail in Chapter 3.

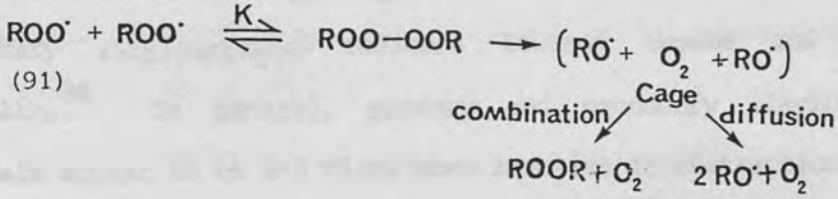
When the debenzoylation was carried out using sodium methoxide under argon, the acid (55), a white solid mpt. 63-68^{o}C, was obtained in excellent yield.

Chapter 3

Structure and Reaction Kinetics of Acyl Nitroxide

(a)β-Disproportionation reaction of acyl nitroxides

Structural factors are important in preventing self-reaction of an organic nitroxide, other than by dimerization at the N-O$^{\bullet}$ centre. The absence or presence of a β-hydrogen can affect the reactivity of nitroxide radicals, however the vast majority of organic nitroxides are unstable because they react with each other through some other centre of the molecule (see Chapter 1). Reactions can occur by hydrogen transfer between two nitroxide radicals at least one of which possesses a β-hydrogen. Removal of the β-hydrogen leads to a nitrone.[34] The initial step involves the reversible formation of a dimer as seen also in the self-reaction of peroxy radicals[36] (scheme 9).



(91)

Scheme 9

The rate constants of hydrogen atom abstraction by free radicals from diamagnetic molecules depend primarily on the activation energy of the reaction. The reaction proceeds rapidly only if the activation energy is small, therefore only exothermic hydrogen abstractions are likely to be fast.[36]

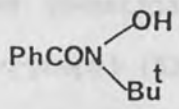
In peroxy radical oxidations involving hydrogen abstraction, the rate is likely to be fast if the ROO-H bond

formed is at least as strong as that which is broken in R-H. Peroxy radicals, which are strongly resonance stabilized, have estimated ROO-H bond strengths of about 90 kcal/mole [Benson],[80] which means that this bond is stronger than a benzylic or allylic C-H bond (84 kcal/mole) or aldehyde C-H bond (86 kcal/mole) allowing rapid hydrogen abstraction in these cases. The bond strength of ROO-H is comparable to a tertiary C-H bond in saturated hydrocarbons (ca. 92kcal/mole), therefore ROO$^{\bullet}$ are comparatively unreactive radicals towards abstraction from saturated hydrocarbons. Hydrogen abstractions by peroxy radicals also exhibit large deuterium kinetic isotope effects.[81]

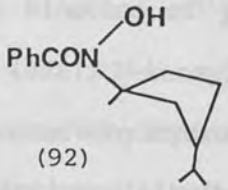
Although R-H bond strength is an important factor in determining rate constants for hydrogen abstraction from R-H, steric and polar effects also play a significant role. For example, tertiary cumylperoxy radicals are less reactive than secondary alkylperoxyl radicals towards cumene and also tetralin.[36] In general, primary and secondary alkylperoxy radicals appear to be 3-5 times more reactive in abstraction than are tertiaryperoxy radicals.

In the acyl nitroxide systems, an important factor in hydrogen abstraction reactions is the NO-H bond strength. Jenkins[51] extended the Ingold equilibrium method,[82] in calculating the NO-H bond strength for a series of substituted N-t-butylbenzohydroxamic acids; and suggested that the 4-dimethylamino- through to the 3,5-dinitro- derivatives should allow a variation in O-H bond strength of about 10 kcal/mole. The insensitivity of the O-H B.D.E. to the steric nature of the alkyl

group has been reported by S.L.Smith[83] in the investigation of a series of alkyls; N-t-butyl (30a) and N-fenchelyl (92) in which a constant B.D.E. of 78.0 kcal/mole was reported.

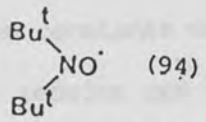


(30a)



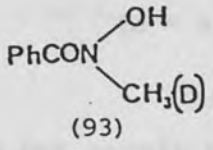
(92)

Extensive work by K.U. Ingold et al[36] and M.J. Perkins et al[63] on the second-order disproportionation reactions of nitroxides and acyl nitroxides respectively have been investigated by e.s.r.. In the case of N-methyl- (93)[63] and N-benzylbenzohydroxamic acids (54),[64] large deuterium kinetic isotope effects indicate the effect of increased B.D.E. of β -hydrogens when replaced by deuterium on the lowering of reaction rates. Rate constants (at 75°C determined by e.s.r.) for hydrogen abstraction by (94) in cumene, ethylbenzene, toluene were found to be 4.9×10^{-4}; 3.02×10^{-4}, and 0.21×10^{-4} $l\,mol^{-1}\,sec^{-1}$: considering toluene to be unity, relative rates per benzylic hydrogen for abstraction from $PhCH_3$, $PhCH_2CH_3$ and $PhCH(CH_3)_2$ 1 : 14.4 : 23.4 reflects the order of donor C-H B.D.E..[84] Equilibrium studies for OH bond of N-t-butylbenzohydroxamic acids (see earlier) ca. 78 kcal/mole implies abstraction from cumene can be only 1 kcal/mole endothermic. Hydrogen abstraction from ethylbenzene or toluene must be correspondingly more endothermic, therefore reactivities of benzylic hydrogens towards acyl nitroxides are ultimately determined by the activation energies for these bimolecular processes.



(94)

As an extension to these studies, work in this thesis included the investigation of the kinetics of β-disproportionation of N-n-propyl (53), N-allyl- (49a), N-benzylbenzohydroxamic acids (54) and N-allyl-N-adamantanecarbonylhydroxylamine (49b). The disproportionation of the N-(primary)alkylhydroxamic acids proved to be cleanly second-order processes by monitoring the radical concentration over 3 1/2 half-lives; such a period allows distinction between first- and second-order reactions by plots of ln C vs. time and 1/C vs. time respectively. The magnitude of the second-order rate constants for the series of compounds might be expected to follow the order (53) < (54) ~ (49a). For (49b), which has an alkanoyl substituent in place of benzoyl, it might be expected that (49b) < (49a), since the PhCON(Bu^t)O-H bond strength is appreciably greater than RCON(Bu^t)O-H [Jenkins].[84b]



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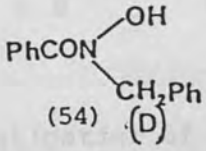


(54)

The actual β-CH bond strengths in these radicals are unknown. The figures given in the Table below are bond dissociation energies for primary CH, benzylic CH, and allylic CH in ethane, toluene, and propene respectively. The values in the nitroxides will be much lower, but the substituent effect should be in the same direction.

The high rate of these reactions and the relative insensitivity of their rates to temperature meant that only very

approximate second-order rate constants were obtained by monitoring the e.s.r. decay. The results are given in TABLE 1 (Fig's 7, 8, 9, 10 show experimental, and simulated spectra, plots of C vs. time and 1/C vs. time respectively for N-benzoyl benzyl nitroxide; a representative example of the N-(primary)alkyl nitroxide radicals studied). The decay of (49a) proved to be too rapid to measure a rate constant by static methods. The reactivity of (49b) is not as predicted, being very much less than for (49a), suggesting that conformational or other factors must be important in determining these reaction rates.

A full discussion of hydrogen abstraction requires knowledge of configuration of both $X^{\bullet}$, $R^{\bullet}$, bond strengths, steric effects and polarity.[85] A linear relationship (Eq. 6) exists between Ea and the strength of C-H bond being broken in hydrogen abstraction reactions by methyl radicals.[86]

$$Ea = \alpha\,[D(R\text{-}H)] + \beta$$

Eq. 6

Time did not permit the investigation of the deuterium isotope effects in the series of compounds. The investigation of second-order rate constants by e.s.r. is difficult, mainly due to problems associated with the measurement of the absolute initial radical concentration. The solution requires the indirect measurement of radical concentration by the use of an internal or external standard radical (see Chapter 7).

Despite the difficulties mentioned, the technique used here for monitoring the rates of reaction is an invaluable one because

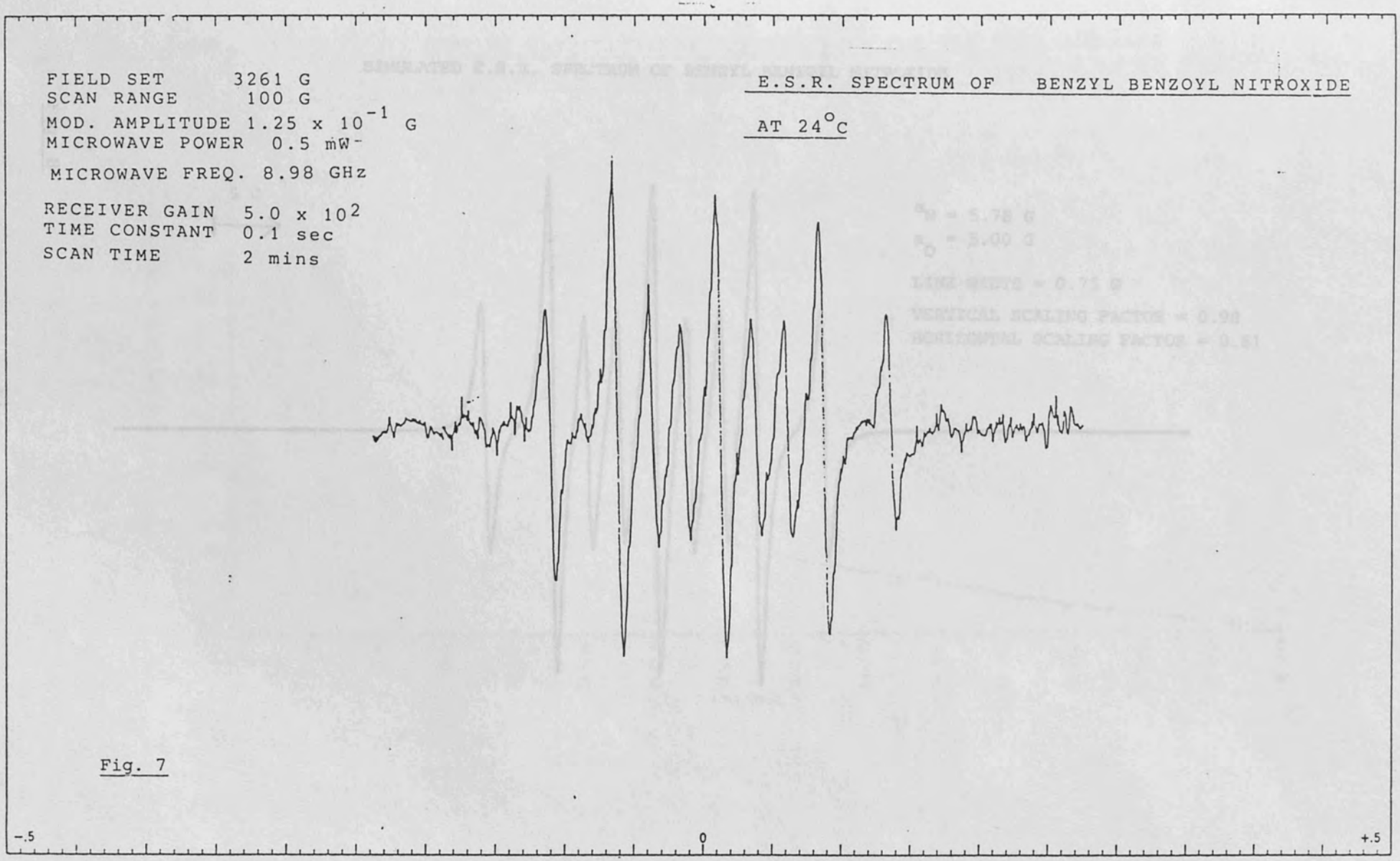
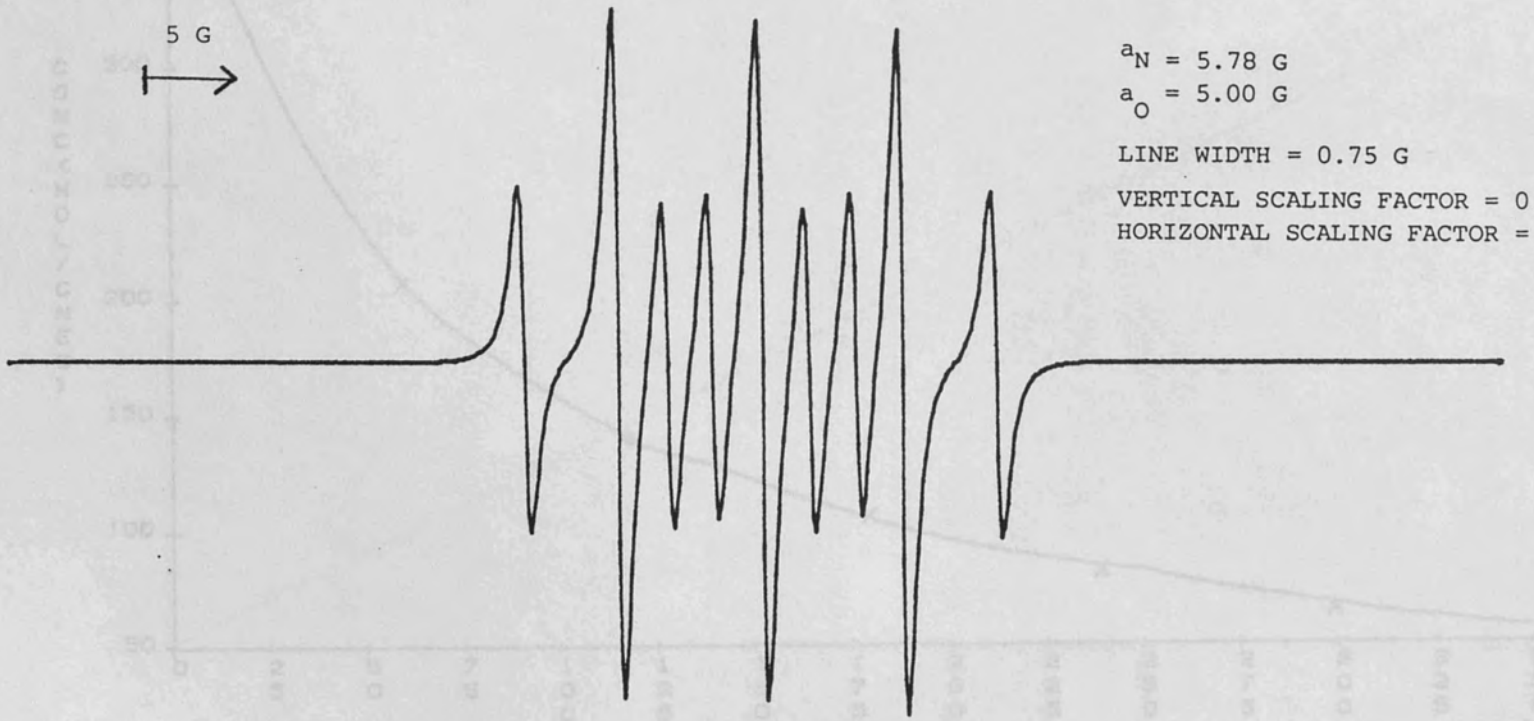

FIELD SET 3261 G
SCAN RANGE 100 G
MOD. AMPLITUDE 1.25 x 10^-1 G
MICROWAVE POWER 0.5 mW
MICROWAVE FREQ. 8.98 GHz
RECEIVER GAIN 5.0 x 10^2
TIME CONSTANT 0.1 sec
SCAN TIME 2 mins
E.S.R. SPECTRUM OF BENZYL BENZOYL NITROXIDE
AT 24°C
-.5
0
+.5

Fig. 7

Fig. 8

SIMULATED E.S.R. SPECTRUM OF BENZYL BENZOYL NITROXIDE



a_N = 5.78 G
a_O = 5.00 G

LINE WIDTH = 0.75 G

VERTICAL SCALING FACTOR = 0.98
HORIZONTAL SCALING FACTOR = 0.81

PLOT OF THE CONCENTRATION VS. TIME FOR THE SELF-REACTION OF N-BENZYL N-BENZOYL NITROXIDE IN t-BUTYL BENZENE AT 24 °C

Fig. 9

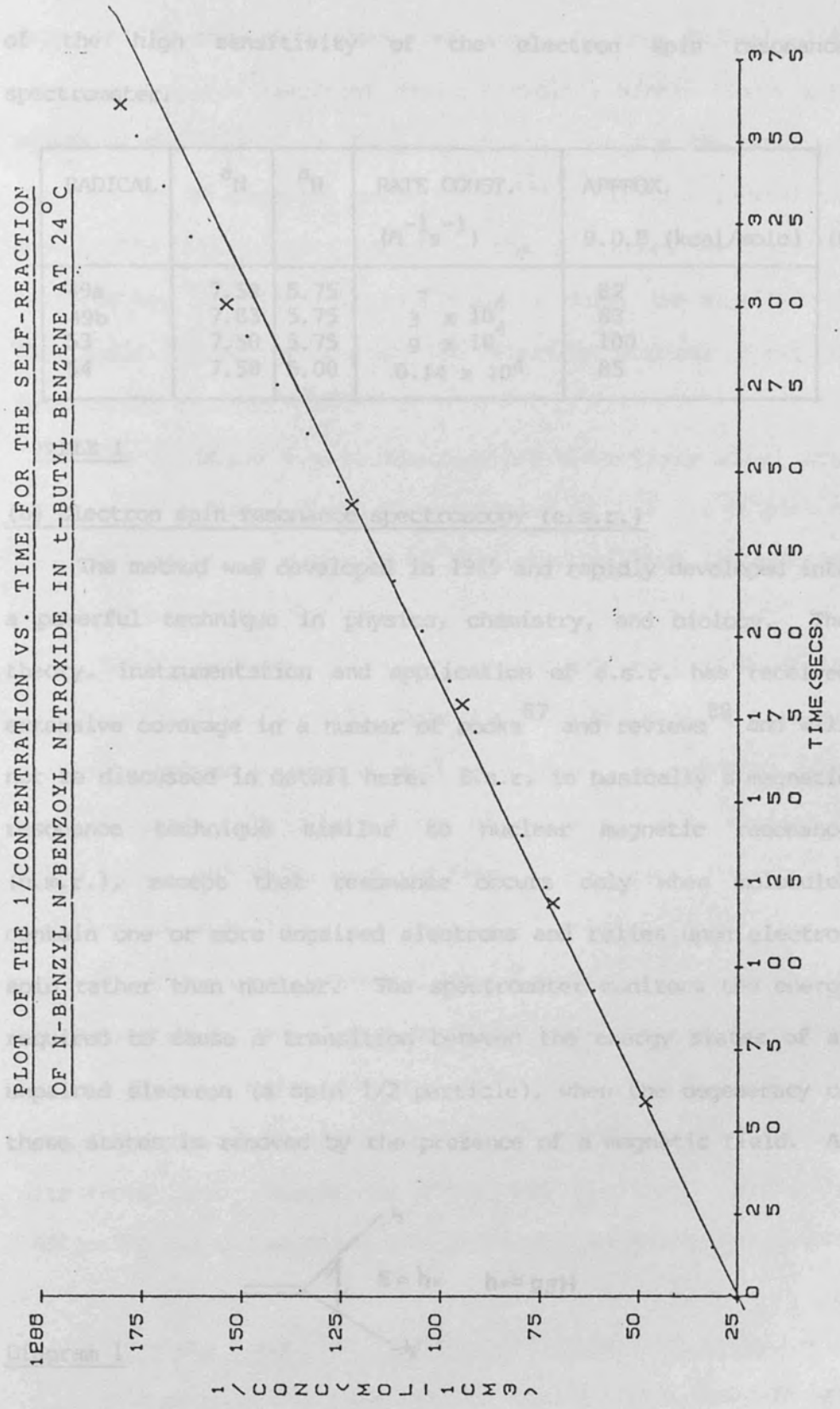

PLOT OF THE 1/CONCENTRATION VS. TIME FOR THE SELF-REACTION
OF N-BENZYL N-BENZOYL NITROXIDE IN t-BUTYL BENZENE AT 24°C
1/CONC (MOL-1 CM3)
1200
175
150
125
100
75
50
25
0
2 5 0
5 0 0
7 5 0
1 0 0 0
1 2 5 0
1 5 0 0
1 7 5 0
2 0 0 0
2 2 5 0
2 5 0 0
2 7 5 0
3 0 0 0
3 2 5 0
3 5 0 0
3 7 5 0
TIME (SECS)

Fig. 10

of the high sensitivity of the electron spin resonance spectrometer.

RADICAL	a_N	a_H	RATE CONST. ($M^{-1}s^{-1}$)	APPROX. B.D.E (kcal/mole)
49a	7.58	5.75	-	82
49b	7.83	5.75	3×10^4	82
53	7.50	5.75	9×10^4	100
54	7.58	5.00	0.14×10^4	85

(SEE TEXT.)

TABLE 1

(b) Electron spin resonance spectroscopy (e.s.r.)

The method was developed in 1945 and rapidly developed into a powerful technique in physics, chemistry, and biology. The theory, instrumentation and application of e.s.r. has received extensive coverage in a number of books[87] and reviews[88] and will not be discussed in detail here. E.s.r. is basically a magnetic resonance technique similar to nuclear magnetic resonance (n.m.r.), except that resonance occurs only when molecules contain one or more unpaired electrons and relies upon electron spin rather than nuclear. The spectrometer monitors the energy required to cause a transition between the energy states of an unpaired electron (a spin 1/2 particle), when the degeneracy of these states is removed by the presence of a magnetic field. As

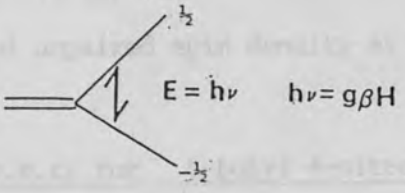


Diagram 1

suggested in diagram 1 above, any spin 1/2 free radical (i.e. with one unpaired electron) should exhibit a single line e.s.r. signal at a frequency defined by $g\beta H/h$. However the effect of the presence of magnetic nuclei (^{1}H, ^{13}C, ^{14}N) in a radical can modify the field experienced by the electron, so that the spectrum may be split into more than one line, the magnitude of the splitting being called the electron nuclear hyperfine interaction constant (^{a}X).

The solution e.s.r. spectrum of a tertiary alkyl acyl nitroxide exhibits a three line spectrum (1 : 1 : 1 triplet of equal intensity) as a result of the interaction of the electron spin with magnetic ^{14}N nuclei.

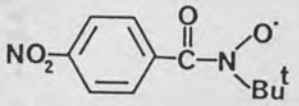
In a secondary alkyl acyl nitroxide each line of the 1 : 1 : 1 triplet is split into doublets by coupling from the single β-hydrogen to give a total of 6 lines. In a primary alkyl acyl nitroxide each of the lines of the 1 : 1 : 1 triplet is split into a triplet by coupling from two equivalent hydrogens to give a total of 9 lines.

^{a}N values were determined from a number of acyl nitroxides after generating the radicals in dilute t-butylbenzene by oxidizing the precusor hydroxamic acid by UV photolytic $H^{\cdot}$ abstraction by di-t-butylperoxide initiator. The ^{a}N values reported for acyl nitroxides are reduced relative to di-t-butyl nitroxide, indicating reduced unpaired spin density at nitrogen (see Chapter 1).

(c) Solid-state e.s.r. for t-butyl 4-nitrobenzoyl nitroxide

Spin density distributions for acyl nitoxide radicals have

been estimated from isotropic solution spectra. Strictly, this only gives information about atomic s-orbital contribution;[87] in the case of (30c) the 2s orbital on N has only 1.4% of total spin



(30c)

density. A fuller picture of atomic spin density can only be derived from anisotropic solid state e.s.r. from which p-orbital spin density can be calculated.

The procedure for calculation of p-spin density requires the simulation of the solid-state e.s.r. spectrum e.g. of (30c). The powder spectrum for the acyl nitroxide (30c) below (Fig. 11) shows three principal features with further structure superimposed on each, and contains information about g_{xx}, g_{yy}, g_{zz}, $A^{N}_{xx}+{}^{a}N$, $A^{N}_{yy}+{}^{a}N$, $A^{N}_{zz}+{}^{a}N$; these arise from the three principal g-values. The general theory involved in solid-state e.s.r. with regards to parameters ($g_{x}...$, $A_{x}....$) has been reviewed in the literature.[89]

The general isotropic solution e.s.r. of an acyl nitroxide (Fig. 12) contains ${}^{a}N$, (${}^{a}H$), g_{iso}. The relationship between g_{iso} and ${}^{a}N$ and their solid-state equivalents are seen below; relationship 1, 2, 3. A_{iso} and g_{iso} are directly obtainable from

Rel. 1 $\quad g_{iso} = 1/3\ (\ g_{xx} + g_{yy} + g_{zz}\ )$

Rel. 2 $\quad {}^{a}N = 1/3\ [\ (A_{xx}{}^{N} + {}^{a}N) + (A_{yy}{}^{N} + {}^{a}N) + (A_{zz}{}^{N} + {}^{a}N)]$

Rel. 3 $\quad Axx + Ayy + A_{zz} = 0$

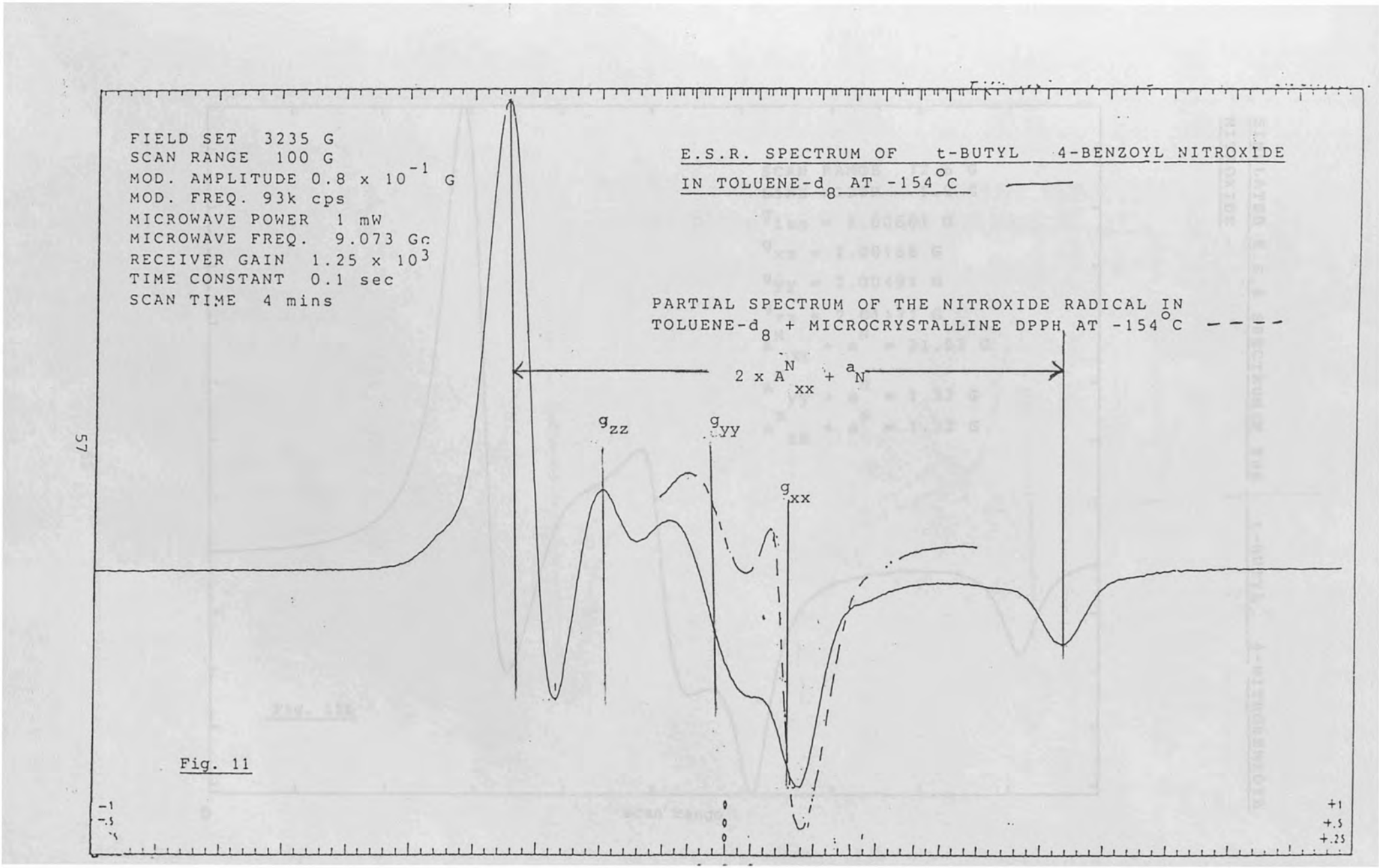

FIELD SET 3235 G
SCAN RANGE 100 G
MOD. AMPLITUDE 0.8 x 10^{-1} G
MOD. FREQ. 93k cps
MICROWAVE POWER 1 mW
MICROWAVE FREQ. 9.073 Gc
RECEIVER GAIN 1.25 x 10^{3}
TIME CONSTANT 0.1 sec
SCAN TIME 4 mins
E.S.R. SPECTRUM OF t-BUTYL 4-BENZOYL NITROXIDE
IN TOLUENE-d_8 AT -154°C
PARTIAL SPECTRUM OF THE NITROXIDE RADICAL IN
TOLUENE-d_8 + MICROCRYSTALLINE DPPH AT -154°C
$2 \times A^{N}_{xx} + a_N$
g_{zz}
g_{yy}
g_{xx}
-1
-.5
0
+1
+.5
+.25

Fig. 11

SIMULATED E.S.R SPECTRUM OF THE t-BUTYL 4-NITROBENZOYL NITROXIDE

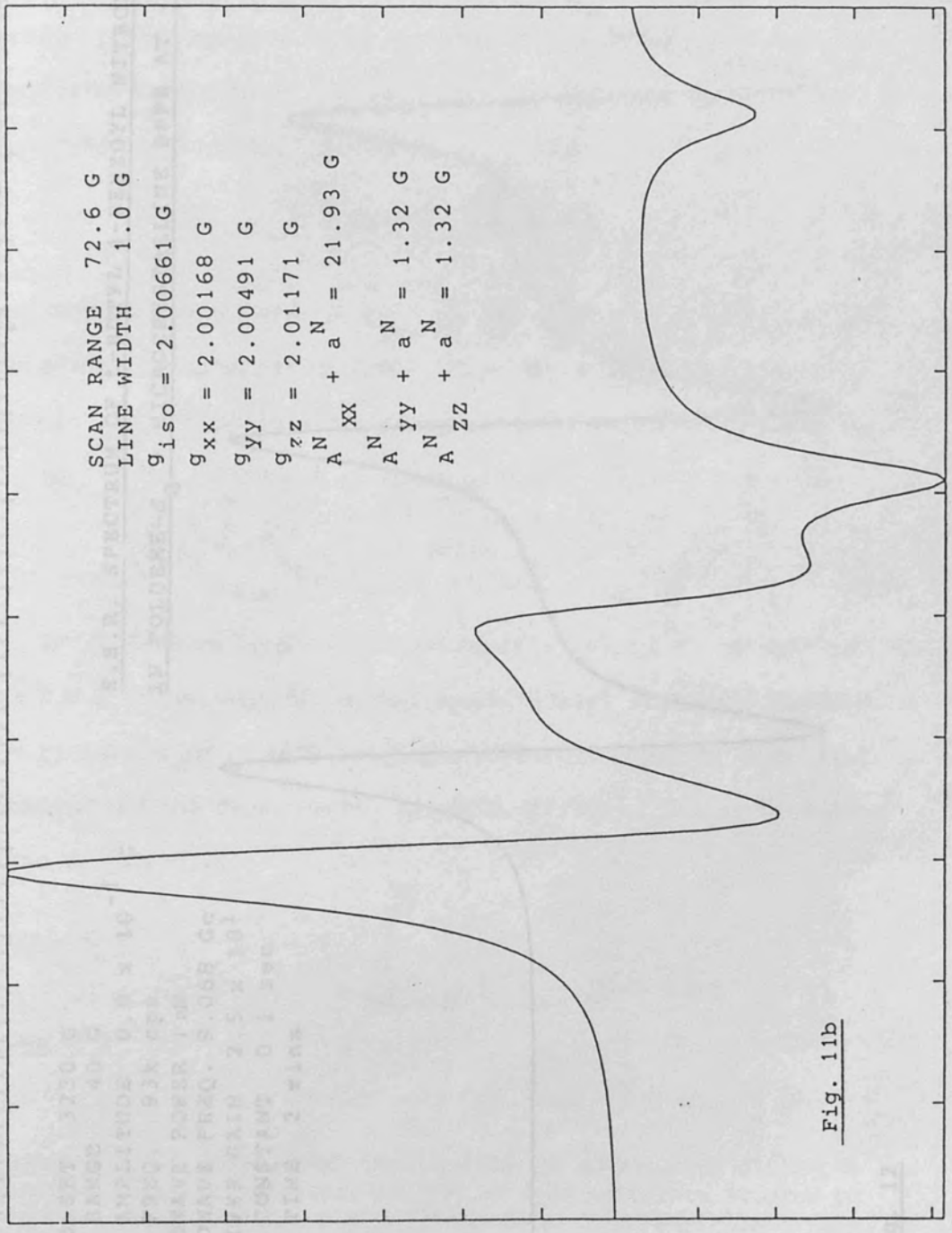


Fig. 11b

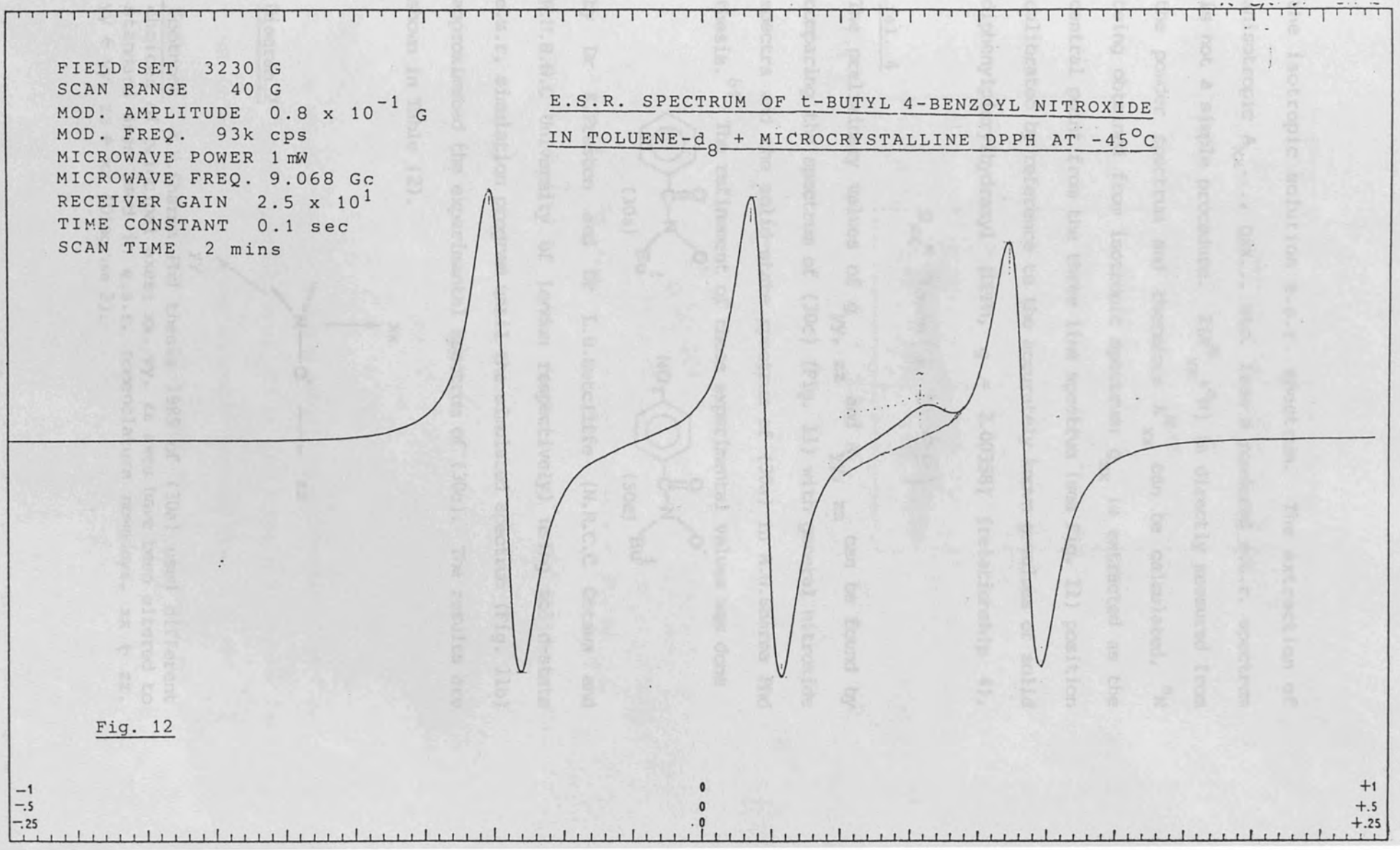

FIELD SET 3230 G
SCAN RANGE 40 G
MOD. AMPLITUDE 0.8 x 10^{-1} G
MOD. FREQ. 93k cps
MICROWAVE POWER 1 mW
MICROWAVE FREQ. 9.068 Gc
RECEIVER GAIN 2.5 x 10^{1}
TIME CONSTANT 0.1 sec
SCAN TIME 2 mins
E.S.R. SPECTRUM OF t-BUTYL 4-BENZOYL NITROXIDE
IN TOLUENE-d_8 + MICROCRYSTALLINE DPPH AT -45°C
−1
−.5
−.25
0
0
.0
+1
+.5
+.25

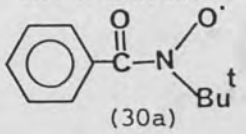
Fig. 12

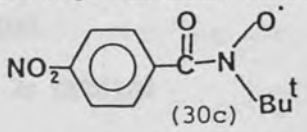
the isotropic solution e.s.r. spectrum. The extraction of anisotropic A_{xx}..., gxx... etc. from a powdered e.s.r. spectrum is not a simple procedure. $2(A^N_{xx}+{}^aN)$ is directly measured from the powder spectrum and therefore A^N_{xx} can be calculated, ^aN being obtained from isotropic spectrum; g_{xx} is extracted as the central point from the three line spectrum (see Fig. 11) position calibrated by reference to the accurately known g-values of solid diphenylpicrylhydrazyl (DPPH, g = 2.00358) (relationship 4).

$$g_{xx} = g_{DPPH}\left(1 \pm \frac{\Delta B}{B}\right)$$

rel. 4

The preliminary values of $g_{yy,\ zz}$ and $A_{yy,\ zz}$ can be found by comparing the spectrum of (30c) (Fig. 11) with general nitroxide spectra and the solid-state spectrum of (30a) in A.H.Sharma Phd thesis.[64] The refinement of these experimental values was done


(30a)


(30c)

by Dr K.Preston and Dr L.H.Sutcliffe (N.R.C.C Ottawa and R.H.B.N.C University of London respectively) using solid-state e.s.r. simulation program until the simulated spectrum (Fig. 11b) approximated the experimental spectrum of (30c). The results are shown in Table (2).

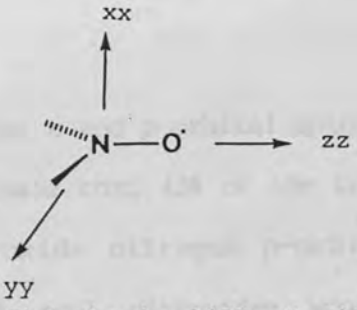


Diagram 2

footnote A.H.Sharma Phd thesis 1985 of (30a) used different choices of principal axes; xx, yy, zz axes have been altered to standard axes used in e.s.r. nomenclature nowadays, xx ← zz, yy ← yy, zz ← xx (Diagram 2).

	(30c) at 120K	(30a) at 77K
g_{xx}	2.00168	2.002
g_{yy}	2.0065	2.006
g_{zz}	2.01171	2.012
g_{iso}	2.0061	2.0061
A_{xx}	14.4	20.7
A_{yy}	6.2	1.6
A_{zz}	6.21	0.00
a^N	7.53	7.4

Table 2

$$\text{spin density } s = \frac{a_{iso}}{A^o} \times 100$$

$$= \frac{7.53}{555.1} \times 100$$

$$= 1.4\% \text{ in 2s orbital}$$

NB. $A^o = {}^aN$ values if 100% spin density at N-atom

$$\rho_\pi{}^N = \frac{A_{xx}{}^N}{A^o} \times 100$$

$$= \frac{14.4}{33.24} \times 100$$

$$= 43\%$$

Fig. 13

In calculating the s and p orbital spin densities (see Fig. 13), the results indicate that 43% of the total spin density is located at the nitroxide nitrogen p-orbital.. ^{13}C and ^{17}O isotopically enriched acyl nitroxides would be required to

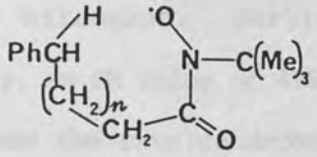
complete a study of p-orbital spin density in these nitroxides. The calculation of s-orbital spin density at nitrogen shows this to be only 1.4% of the total spin density, this indicates that the representation of the distribution of spin density at oxygen and nitrogen in acyl nitroxide using isotropic e.s.r. was probably the distribution of no more than 10% of the total spin densities, and therefore an inadequate representation of the spin distribution.

Intramolecular hydrogen abstraction and radical-addition reaction

The increased reactivity associated with acyl nitroxides compared with alkyl nitroxides has allowed the investigation of the enhanced reactivity of intramolecular radical reactions over intermolecular reactions. Until now this has only been investigated for hydrogen abstraction reactions.

Several different methods of measuring the intramolecular kinetics reactivity of ionic and radical species have been proposed, many of such methods only allow comparison between species which undergo reactions via similar mechanisms. For example, the measurement of the "effective molarities" (EM's) for intramolecular reactions allow us to compare the efficiencies of different classes of intramolecular reactions. This topic has been reviewed extensively by Page and Jencks[90] and Kirby[91] in which the terms "loose" and "tight" transition states are introduced. This reveals the differences between intramolecular nucleophilic catalysis and the mechanism involving intramolecular acid/base catalysis, EM values for acid/base catalysis which

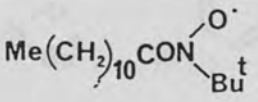
involved proton transfer generally have EM < 10 M this being associated with loose transition states, whereas enormous EM $\geq 10^5$ M for intramolecular nucleophilic reactions are associated with tight transition states. It is found that the degree of bond formation/deformation in the transition states (T.S.) is a major contributor to a high EM value and the degree of flexibility of T.S. - whether T.S. is tight or loose.[90] Hydrogen abstraction reactions in a series of ω-phenyl-alkanoyl t-butyl



(95)

n-	EM
0	0.45
1	1.3
2	1.2
3	0.03

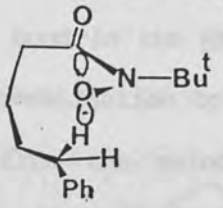
nitroxides (95) n = 0-3 have been reported by Perkins et al.[61] These intramolecular hydrogen transfers to oxygen from the benzylic position occur most readily when n = 1 or 2; in these cases - 1,6 and 1,7 hydrogen shifts respectively - these reactions are first-order in nitroxide. When rate constants were compared with



(96)

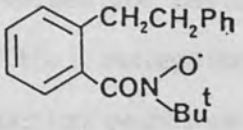
intermolecular hydrogen abstraction from ethylbenzene by (96) the reactivities can be expressed as EM values and range between 0.45-1.3 M. An interesting result was that the reaction via an 8-membered T.S. ring is favoured over the more familar 6-membered ring. This was explained by the most favourable delivery of

benzylic hydrogen on to a p-orbital lobe at nitroxide oxygen when n = 2 in a structure retaining an essentially planar carbonyl nitroxide unit. In such systems greater rate enhancement is found when the benzylic system was constrained in closer proximity

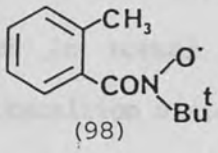


(95b)

with the nitroxide. Perkins et al[50] have shown increased reactivity, an EM value of 496 M for (97). It is evident that in such a case the rate enhancement is due to tighter T.S. in (97) than in (95), mainly due to a more favourably placed nitroxide radical, where an 8-membered T.S. is again favourable. The system (97) shows the highest EM value reported for hydrogen abstraction reaction in nitroxide system[62] (other examples have also been reported by Grimes,[62] for example (98)) this may also



(97)

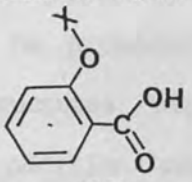


(98)

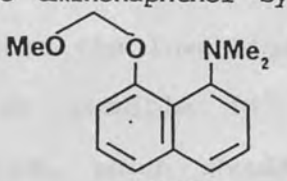
involve a tighter T.S. than (95), but it is still loose.

Recent investigations have indicated that general acid/base catalysis in enzymic reactions are very much more efficient than in simple intramolecular systems. Kirby and co-workers[92,93] have indicated that such large differences are not intrinsic in the simple system but depend on the degree of bond formation during

proton transfer, i.e. tightness of the bonds in the T.S.. In the case of salicylic acid derivatives (99) [where X = $CHROR^1$,[94] PO_3^{2-},[95] SO_3^-,[96]] EM values up to 10^5 M have been attained; such values, it is concluded, are dependent on the strong intramolecular hydrogen bond in the product anion (101). Kirby et al[93] extended this investigation to the hydrolysis of methoxy methyl acetal derived from the aminonaphthol system (100) in



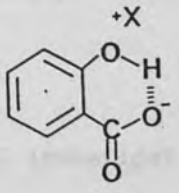
(99)



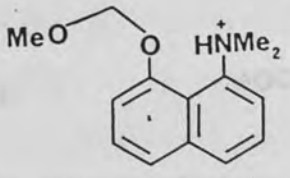
(100)

which reaction below pH 1 is 1000 times faster than at pH 9-10, this being consistent with catalysis of reaction by Me_2NH (102). It is concluded that the thermodynamic stabilization of leaving group derived from strong intramolecular H-bonds of (101) and (102) is reflected in the T.S. for acetal cleavage - six-membered T.S., and therefore reflected in kinetic parameters.

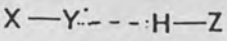
High EM values for salicyclic acid derivatives (99) can be explained by the assumption that in normal intramolecular hydrogen abstraction reactions the transition states involved are linear,[97] for example (103); this geometry can be attained only in large cyclic T.S. where formation of ring or cyclic T.S. per se are enthalpically neutral or diffusion-controlled, and



(101)



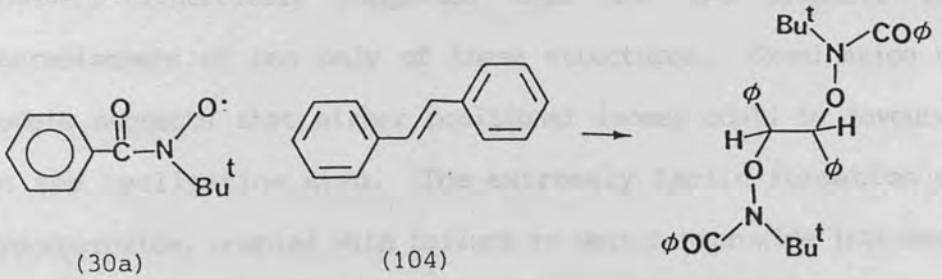
(102)



(103)

therefore reactions are entropically driven. Whereas in the formation of small or medium size rings or cyclic T.S.'s the EM's are above the norm (as seen in the case of (99)) and may indeed be dominated by enthalpy of formation of the cyclic ring.[97]

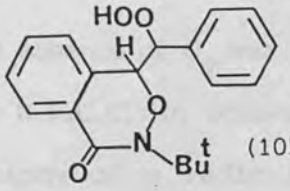
It can be proposed that the investigation of more constrained structures may be possible in intramolecular radical-alkene addition reaction, which should have values approaching calculated maximum EM value 10^8 M (10^{13} M in strained systems [Page and Jencks][90]) due to tighter T.S. than hydrogen abstraction reactions. The examples of measured EM values for intramolecular radical-alkene reaction in the literature are limited. To investigate this, oxidation of the trans-stilbene hydroxamic acid (55) was studied. The intermolecular reaction of (30a) with a double bond (104) has been previously investigated by N.P.Y. Siew[30] and other workers,[84b] where rates were very slow, this being associated with steric hindrance of bulky phenyl groups in stilbene.



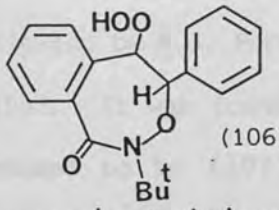
(30a) (104)

Initial investigations of the one-electron oxidation of the

"stilbene hydroxamic acid" (55) showed no evidence of nitroxide formation. However, a reaction did take place and a colourless crystalline product was obtained in low yield. Further study showed that (55), dissolved in $CDCl_3$, when left to stand in the presence of air, is slowly and quantitatively transformed into two new products, one of which had a ^1H n.m.r. spectrum identical with that of the colourless product reported above. The two products were chromatographically indistinguishable (t.l.c.) and co-crystallized. Only on repeated crystallization was a pure compound (98% as judge by t-butyl resonance) isolated, again in poor yield. However, both the purified material, and a solid fraction containing ca. 30% of the second compound gave microanalytical figures consistent with the formation of a hydroperoxide (105) or (106). These structures were supported by mass



(105)

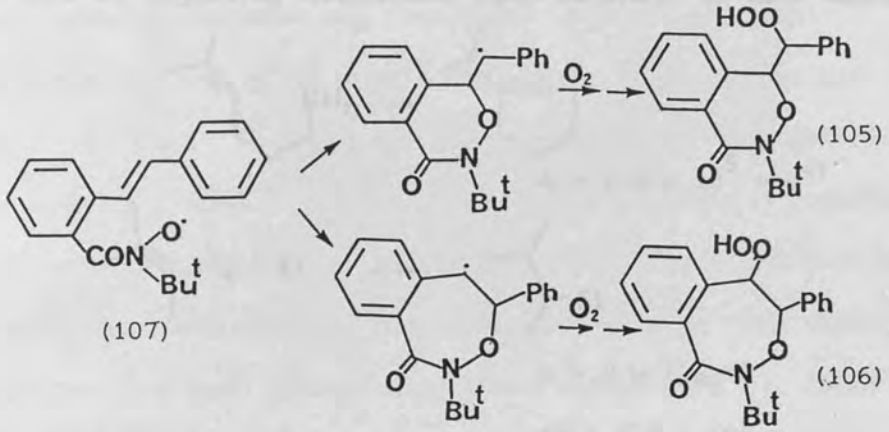


(106)

spectroscopy, but no simple spectroscopic technique allowed a distinction to be made between the two possiblities. It is, however, tentatively suggested that the two products are stereoisomers of one only of these structures. Examination of Models suggests that either positional isomer could be favoured in the cyclization step. The extremely facile formation of hydroperoxide, coupled with failure to detect nitroxide intermediates by e.s.r. suggests that cyclization of the nitroxide on the stilbene double bond is indeed extremely rapid. The proposed

route to hydroperoxide formation is shown in (scheme 10). Attempts were made to obtain a sample of the pure hydroperoxide suitable for X-ray crystallography, but these were unsuccessful. Degradation studies have not yet been carried out.

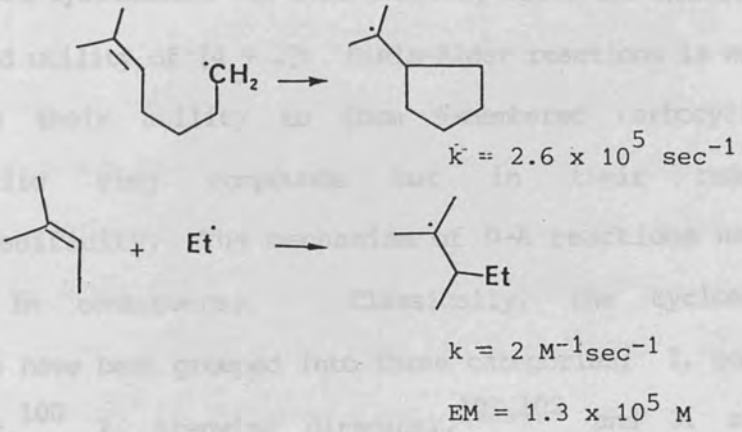
The formation and decay of the proposed nitroxide intermed-



Scheme 10

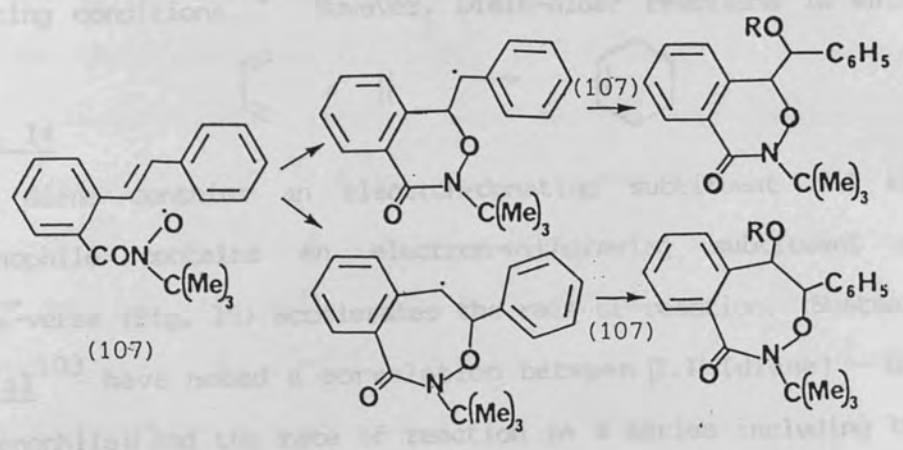
iate in the absence of O_2 was investigated by M.J. Perkins during a visit to N.R.C.C. in Ottawa in 1987. It was found that high concentrations of a radical, assumed to be (107) could be obtained by UV photolysis of a solution of di-t-butyl peroxide in t-butylbenzene containing (55) at temperatures below ca. $-10^{o}C$, but that when the UV source was shuttered the radical decayed rapidly with first-order kinetics with Arrhenius parameters Ea = 12.8 kcal/mole and $A = 6 \times 10^{9}\ s^{-1}$. The model reaction of $PhCON(Bu^{t})O^{\bullet}$ and trans-stilbene was studied at $+120^{o}C$, and extrapolation of rate data for (107) gave $EM = 5 \times 10^{5}$ M. Although intramolecular radical additions are generally believed to be rapid, this is one of the first in which direct rate

comparison with an intermolecular model has been made. It is also unusual in that the rapid reaction leads to a six- or seven-membered ring. The only example found in the literature depended on separately published data for intra- and inter-molecular reactions (scheme 11), the calculated EM 1.3 x 10^5 M depended on adjusting literature rate constant to take account



Scheme 11

of more recent reference values.[98] The products of the intra-molecular radical addition of (107) in the absence of O_2 is expected to be similar to the 1 : 2 adduct proposed by N.P.Y. Siew[30] for intermolecular system (scheme 12).



Scheme 12

Chapter 4

Cycloaddition and retrocycloaddition of acyl nitrones.

(A) Introduction Diels-Alder reactions

Reaction between a conjugated diene and an alkene (the dienophile, which is also usually conjugated) to form a substituted cyclohexene was formulated by Diels and Alder.[99] The widespread utility of [4 + 2]π Diels-Alder reactions is not only found in their ability to form 6-membered carbocyclic or heterocyclic ring compounds but in their remarkable stereospecificity. The mechanism of D-A reactions has been covered in controversy. Classically, the cycloaddition reactions have been grouped into three categories; 1. concerted reactions,[100] 2. stepwise diradical,[101,102] and 3. stepwise zwitterion.[101,102]

There is considerable variation in the ease with which allowed D-A reactions can take place. The prototype reaction of s-cis butadiene with ethene (Fig. 14) is very slow and requires forcing conditions.[99] However, Diels-Alder reactions in which

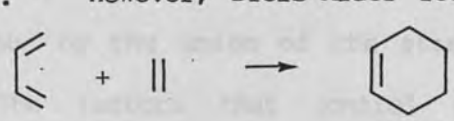
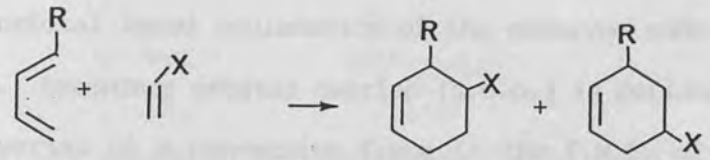


Fig. 14

the diene contains an electron-donating subtituent and the dienophile contains an electron-withdrawing subtituent or vice-versa (Fig. 15) accelerates the rate of reaction. Sustmann et al[103] have noted a correlation between [I.P (diene) - E.A (dienophile)]* and the rate of reaction in a series including two dienophiles and an extensive series of dienes. In the

*I.P. = ionization potential, E.A. = electron affinity

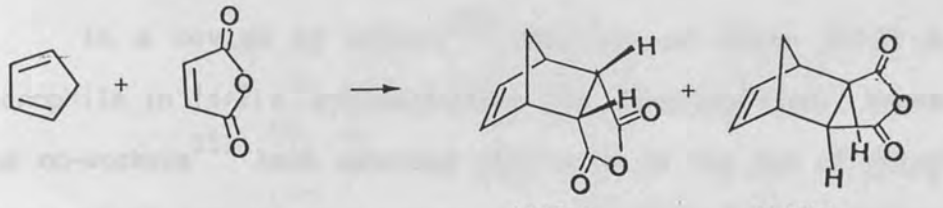
Diels-Alder reaction of unsymmetrically substituted diene (108) and dienophile (109) it is found that one isomer is favoured, the explanation lies within F.M.O. (frontier molecular orbital) theory.



(108) (109) MAJOR MINOR

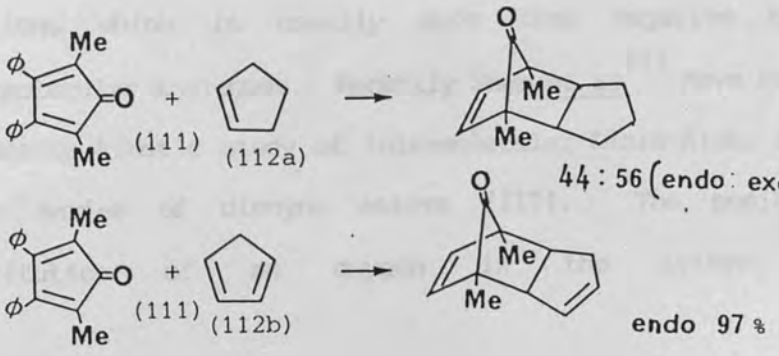
Normal Diels-Alder reaction transition states have highly stabilized diene HOMO - dienophile LUMO interactions; electron rich alkenes are unreactive with simple dienes due to the absence of a strong stabilizing interaction. Diels-Alder reactions with inverse electron demand arise when the diene LUMO - dienophile HOMO interaction is greatest, so electron donation on the dienophile accelerates the reaction rate.

The explanation of the regioselectivity can be interpreted by the application of F.M.O. concepts in which the controlling factor is found in the frontier orbital co-efficients in the HOMO and LUMO of the diene and dienophile. The favoured cycloadduct will be that formed by the union of the atoms with largest co-efficients. The factors that control the regio- and stereochemistry of Diels-Alder reactions have been extensively reviewed.[103] In the cycloaddition of dienes and dienophiles where bridged compounds result e.g. (110), two geometrical isomers endo and exo result. In many examples it is known that endo adducts are formed preferentially when conducted under kinetic control. This is the Alder "endo" Rule. Woodward and Hoffmann[104] proposed that secondary orbital overlap provided a



(110a) (110b)

molecular orbital based explanation of the observed endo stereo-preference. Secondary orbital overlap (s.o.o.) is defined as the positive overlap of a non-active frame in the F.M.O. of a peri-cyclic reaction. Although the observed preference under kinetic control for endo adducts can be explained by s.o.o.,[104,105] in many reactions steric interactions are said to be of equal importance,[106,107] both factors can act at the same time. Houk et al[108] has differentiated between these factors experimentally by the reaction of a subtituted cyclopentadienone (111) and cyclopentadiene (112b) or cyclopentene (112a). The presence of an extra double bond allowing for s.o.o. was found to transform a non-selective process into a selective one. The energy difference between the two T.S's, a measure of the importance of s.o.o. was 2.5-5.0 kcal/mole. The importance of s.o.o. and steric interaction in the reaction of fulvene with cyclopentene or maleic anhydride using MNDO and AM1 SCF semi-empirical calculations have been reported by Fox et al.[109]



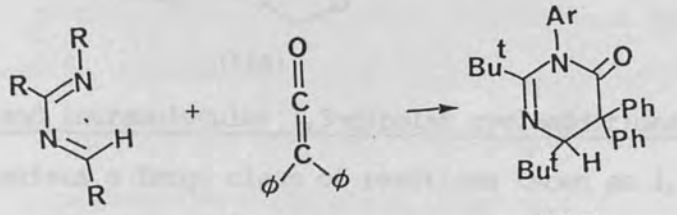
(111) (112a) 44 : 56 (endo : exo)

(111) (112b) endo 97 %

In a review by Alder,[110] the use of imine (113) as dienophile in [4+2] π cycloadditions has been reported. Kresze and co-workers[111] have extended this work in the use of N-acyl imine (114) and iminium salts, demonstrating the generality

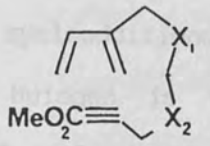
(113) (114)

of electron deficient imino- species in Diels-Alder reactions. Recent advances have included the cycloaddition reactions of 1,3-diazabutadienes (115) with diphenylketene (116).[112]



(115) (116)

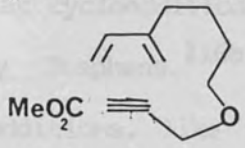
The scope and mechanism of intramolecular Diels-Alder reactions have been reviewed.[113] [4+2] π intramolecular Diels-Alder cycloaddition reactions may vary from the usual intermolecular patterns, for example, even those involving unactivated dienophiles such as unactivated carbon-carbon multiple bonds can occur smoothly. This results from the influence of the entropic factors ($\Delta S^{\neq}$) for intramolecular reactions which is usually much less negative than for intermolecular analogues. Recently Shea et al[114] have reported a systematic kinetic study of intramolecular Diels-Alder reactions of a series of dienyne esters (117). The positions of substitution of an oxygen in the tether between



a $X_1 = X_2 = CH_2$
b $X_1 = O, X_2 = CH_2$
c $X_1 = CH_2, X_2 = O$

(117)

diene and dienophile results in substantial rate differences, relative rates a : b : c are 62 : 1 : 1. The variation of tether chain length from 5 to 7 atoms also produces changes in both enthalpy and entropies of activation, for example (118).



(118)

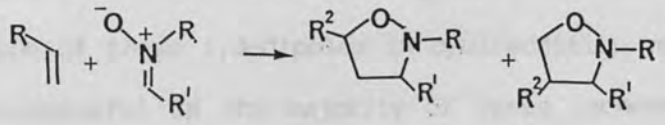
(B) Inter- and intramolecular 1,3-dipolar cycloadditions

There exists a large class of reactions known as 1,3-dipolar cycloadditions reactions analogous to the $[4+2]_\pi$ Diels-Alder reactions. Variation in the structure in both the 1,3-dipole and dipolarophile makes this a very versatile and useful reaction in the synthesis of five-membered ring (Fig. 16) heterocycles. A 1,3-dipole is basically a system of three atoms over which are distributed four π-electrons as in the allyl anion system. The three atoms can be a wide variety of combinations of C, O, and N. Hu sigen et al have studied the mechanism of

Fig. 16

1,3-dipolar cycloadditions extensively.[115] The mechanism proposed by Huisgen is that of a single-step four centre "no-mechanism" cycloaddition in which the two new bonds are both partially formed in the T.S., although not necessarily to the same extent. An alternative mechanism has been proposed by Firestone et al[116a] in which biradical or zwitterion intermediates exist. Evidence about structure of the transition state of 1,3-dipolar cycloaddition using Hammett experiments has been reported by Stephens.[116b] The regioselectivity of 1,3-dipolar cycloadditions, like that of analogous Diels-Alder reactions, can be rationalized based on the concerted T.S. model in which both electronic and steric effects[117] are involved. Houk et al[118] proposed an explanation based upon F.M.O. that in the general case the dipole LUMO - dipolarophile HOMO is the predominant interaction.

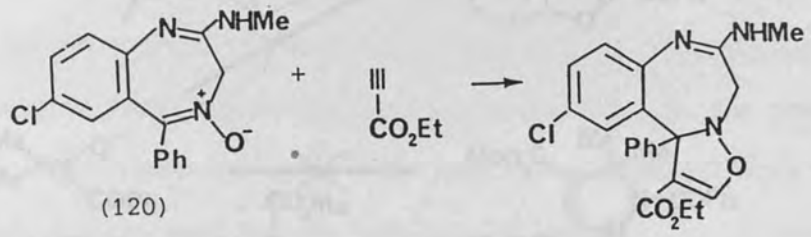
Nitrones (119) are known to react as 1,3-dipoles and undergo cycloaddition with alkenes to produce isoxazolidines. When the reaction involves unsymmetrical alkenes or alkynes, the usual result is a 5-substituted adduct in which the nitrone oxygen terminus is linked to the unsubstituted alkene carbon. Huisgen found that an exception to this rule is the reaction of nitrones



(119)

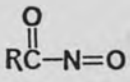
with electron-deficient acetylenes,[119] in which case

4-substituted isoxazolidines predominate (i.e. in this case dipole HOMO - dipolarophile LUMO is the predominant interaction). Another way to reverse regioselectivity of addition by decreasing nitrone HOMO - dipolarophile LUMO interaction is by making the nitrone electron rich. For example, 1,3-dipolar cycloaddition of the 1,4-benzodiazepinic nitrone (120) with ethyl propiolate led exclusively to 4-isomer.[120] The electron-donating effect is due to the disubstitution on the C-terminus and also to the amidine functional group.



(120)

A hetero-Diels-Alder reaction achieved by Kirby and Sweeny[121] involved the cycloaddition of transient acyl nitroso compounds to dienes, e.g. the nitroso-compound (121) formed by

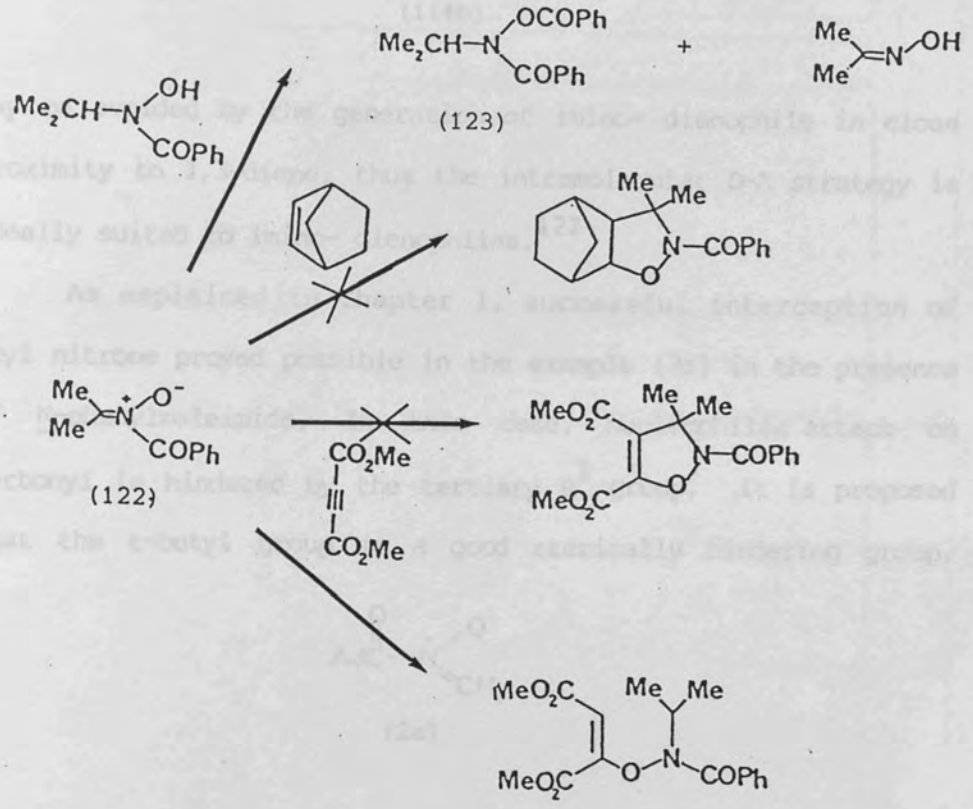


(121)

oxidation of benzohydroxamic acid. N-Alkylhydroxamic acids may be oxidized via nitroxides to N-acyl nitrones, but the interception of these 1,3-dipoles in cycloaddition reactions has proved unsuccessful in the majority of cases (scheme 13). The difficulty seemed to be associated with the high susceptibility of the carbonyl group to nucleophilic attack. Thus (122)

acylates precursor hydroxamic acid to give (123) and acetone oxime.[65]

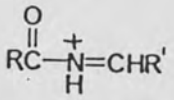
At least two possible approaches may increase the likelihood of cycloaddition. Firstly, steric hindrance at the carbonyl



Scheme 13

group (see Chapter 1) and secondly intramolecular interception. As seen in the cycloaddition of N-acyl imines, lack of interest in acyl nitrones by the synthetic community is due to their reactive nature. All types of imines are rapidly hydrolysed in

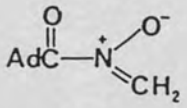
the presence of traces of water; the structure of the N-acyl nitrone can be compared with N-acyl imine (114b)[111] in terms of its carbonyl reactivity. The side reactions of imines



(114b)

may be avoided by the generation of imino- dienophile in close proximity to 1,3-diene, thus the intramolecular D-A strategy is ideally suited to imino- dienophiles.[122]

As explained in Chapter 1, successful interception of acyl nitrone proved possible in the example (2a) in the presence of N-phenylmaleimide, in this case, nucleophilic attack on carbonyl is hindered by the tertiary R^1 group. It is proposed that the t-butyl group is a good sterically hindering group,



(2a)

therefore this should allow interception by N-phenylmaleimide and other similar dipolarophiles. From thermodynamic and kinetic data of the hydrolysis of 1-adamantylcarboxylate and pivalate[123] it is reported that, the 1-adamantyl group has roughly 1 kcal/mole more steric hindrance than t-butyl group.

The cycloaddition of (2a) to N-phenylmaleimide was repeated, and the ^1H n.m.r. spectrum of the adduct was recorded at 400MHz

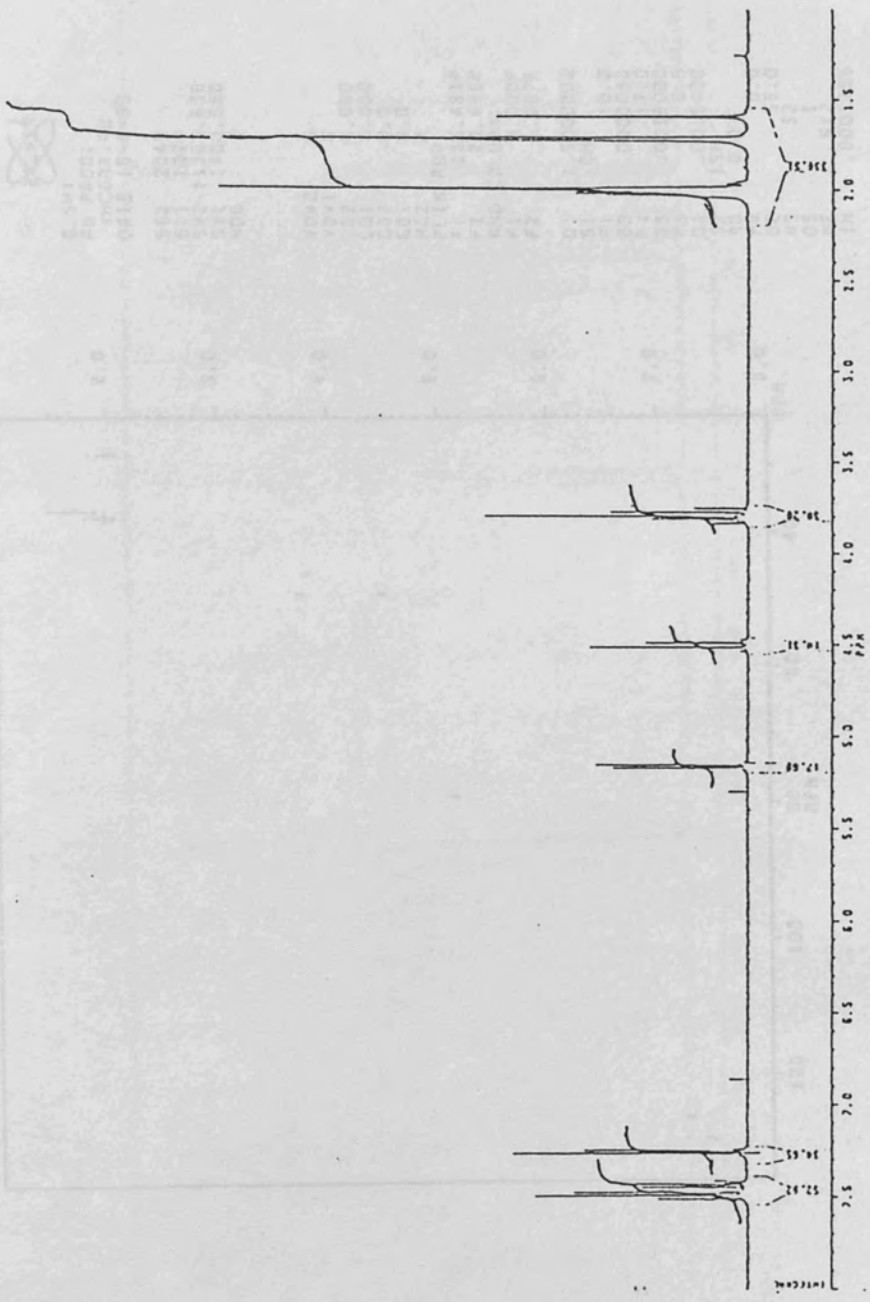


Fig. 17a

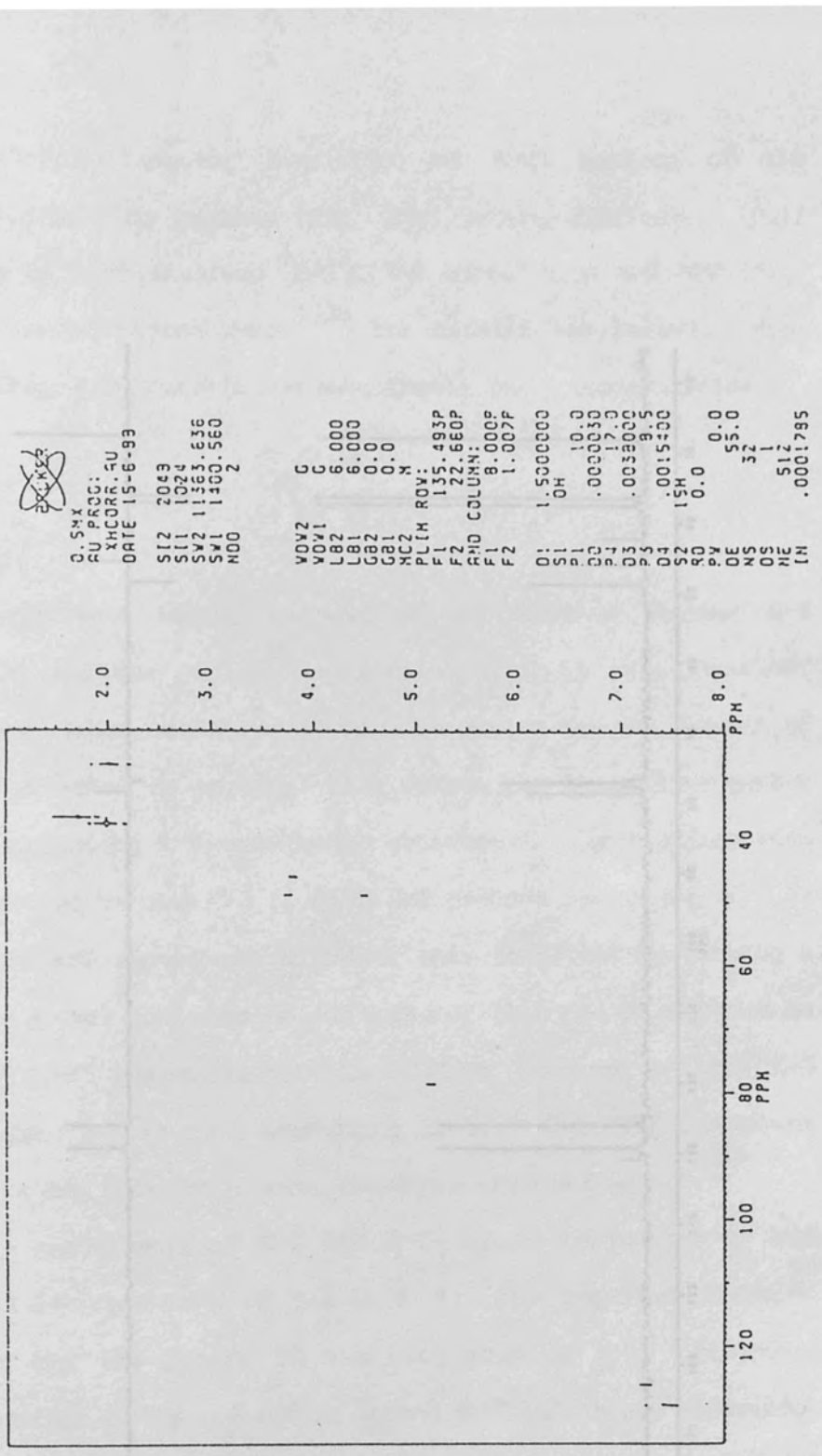


Fig. 17c

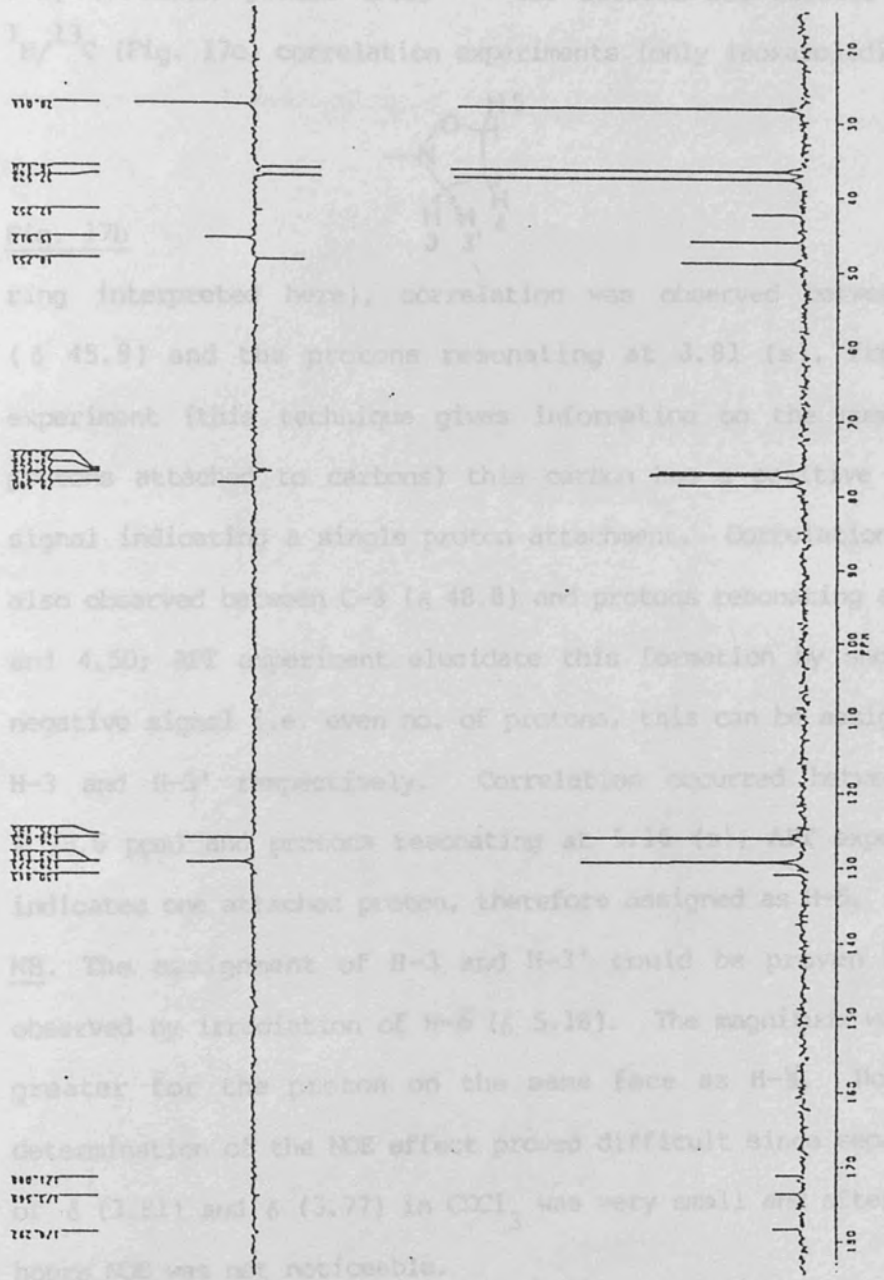


Fig. 17d

(Fig. 17a). Computer simulation of ABMX pattern of the isoxazolidine ring protons (Fig. 17b) proved difficult. Full analysis of this involved $^{1}H/^{13}C$ 2-D correlation and APT (Fig. 17d) (attached proton test,[123b] for details see below). From $^{1}H/^{13}C$ (Fig. 17c) correlation experiments (only isoxazolidine

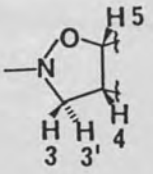


Fig. 17b

ring interpreted here), correlation was observed between C-4 (δ 45.9) and the protons resonating at 3.81 (s), from APT experiment (this technique gives information on the number of protons attached to carbons) this carbon has a positive carbon signal indicating a single proton attachment. Correlations were also observed between C-3 (δ 48.8) and protons resonating at 3.77 and 4.50; APT experiment elucidate this formation by showing a negative signal i.e. even no. of protons, this can be assigned as H-3 and H-3' respectively. Correlation occurred between C-5 (δ 78.6 ppm) and protons resonating at 5.16 (s), APT experiment indicates one attached proton, therefore assigned as H-5.

NB. The assignment of H-3 and H-3' could be proven by NOE observed by irradiation of H-5 (δ 5.16). The magnitude would be greater for the proton on the same face as H-5. However, determination of the NOE effect proved difficult since separation of δ (3.81) and δ (3.77) in $CDCl_3$ was very small and after 1 1/2 hours NOE was not noticeable.

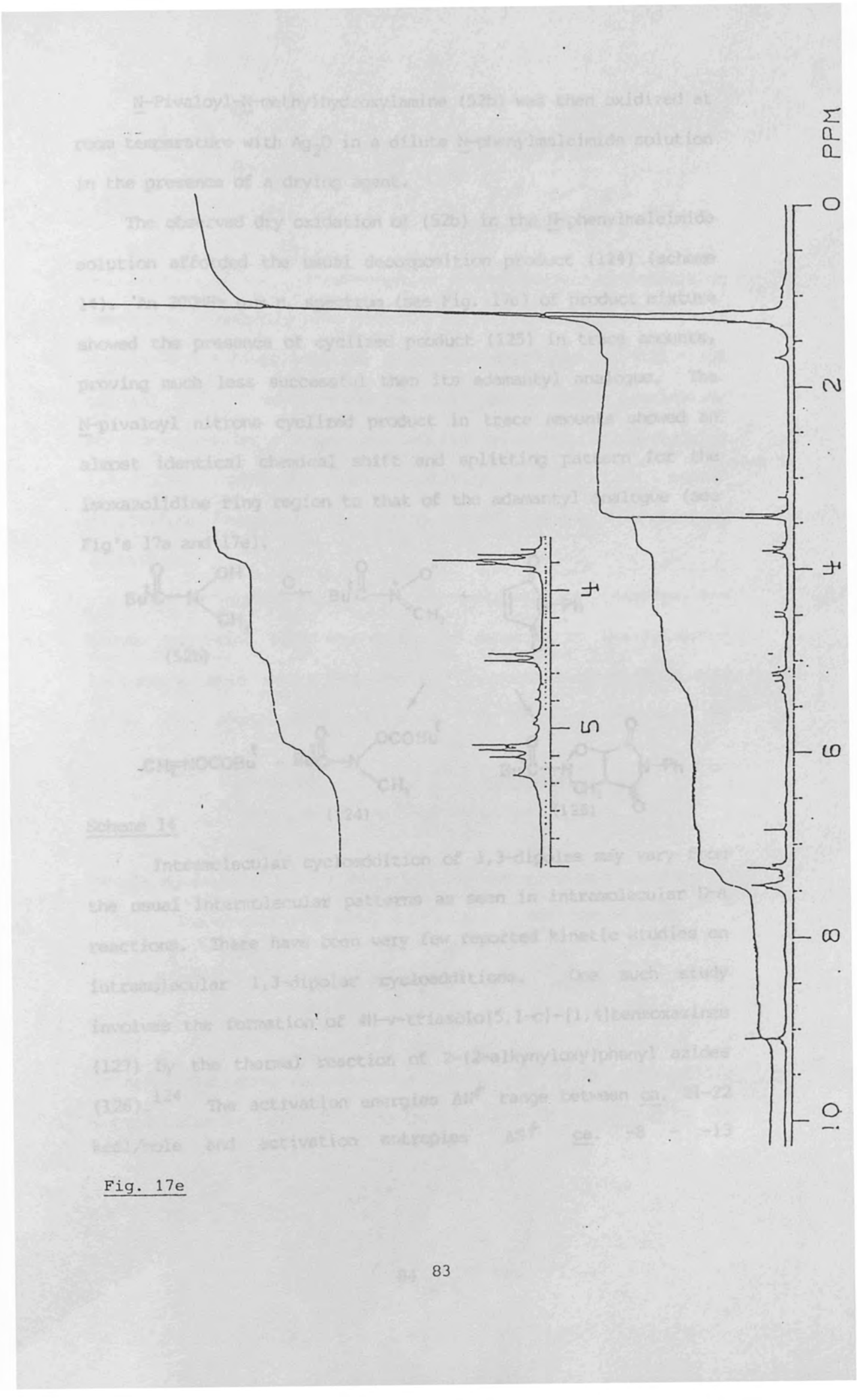
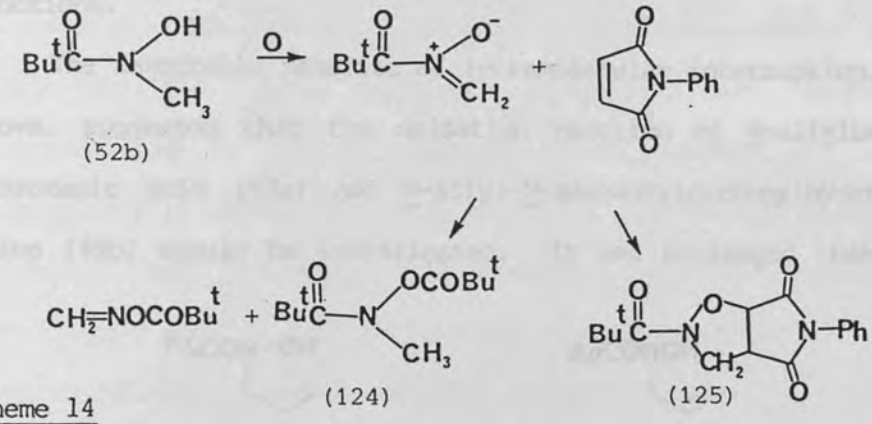


Fig. 17e

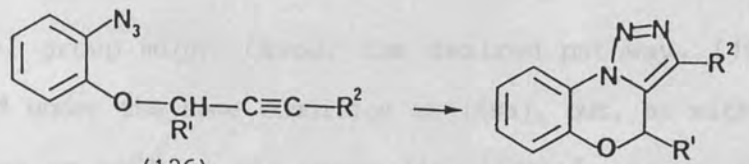
N-Pivaloyl-N-methylhydroxylamine (52b) was then oxidized at room temperature with Ag_2O in a dilute N-phenylmaleimide solution in the presence of a drying agent.

The observed dry oxidation of (52b) in the N-phenylmaleimide solution afforded the usual decomposition product (124) (scheme 14). An 200MHz n.m.r. spectrum (see Fig. 17e) of product mixture showed the presence of cyclized product (125) in trace amounts, proving much less successful than its adamantyl analogue. The N-pivaloyl nitrone cyclized product in trace amounts showed an almost identical chemical shift and splitting pattern for the isoxazolidine ring region to that of the adamantyl analogue (see Fig's 17a and 17e).



Scheme 14

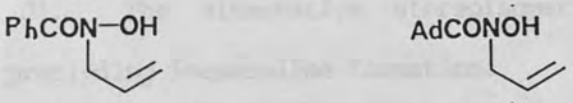
Intramolecular cycloaddition of 1,3-dipoles may vary from the usual intermolecular patterns as seen in intramolecular D-A reactions. There have been very few reported kinetic studies on intramolecular 1,3-dipolar cycloadditions. One such study involves the formation of 4H-v-triazolo[5,1-c]-[1,4]benzoxazines (127) by the thermal reaction of 2-(2-alkynyloxy)phenyl azides (126).[124] The activation energies $\Delta H^{\neq}$ range between ca. 21-22 kcal/mole and activation entropies $\Delta S^{\neq}$ ca. -8 - -13



(126) (127)

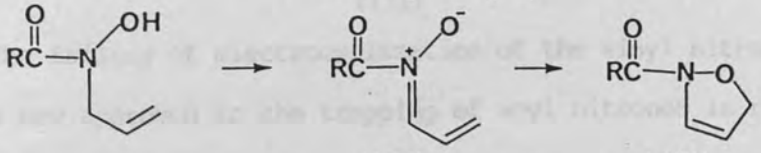
cal mol^{-1} K^{-1}. Intermolecular 1,3-dipolar cycloaddition reactions normally have moderate activation energies $\Delta H^{\neq}$ 10-17 kcal/mole and large negative activation entropies $\Delta S^{\neq}$ -26 - -36 cal $mol^{-1}K^{-1}$. These changes represent going from a bimolecular to a unimolecular process; the results prove that intramolecular 1,3-dipolar cycloadditions essentially profit from steric constraints favourable to bonding contact between the reacting functions.

The favourable benefits of intramolecular interception, see above, suggested that the oxidation reaction of N-allylbenzohydroxamic acid (49a) and N-allyl-N-adamantylcarbonylhydroxylamine (49b) should be investigated. It was envisaged that the



(49a) (49b)

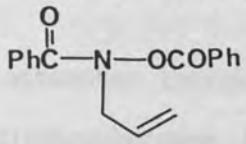
resulting acyl nitrone (128) might undergo electrocyclization to (129). The oxidation of (49a) (Ag_2O; CH_2Cl_2; room temperature)



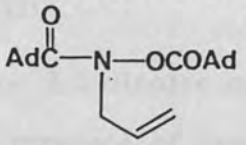
(128) (129)

afforded the usual decomposition product (130a) by nucleophilic substitution at carbonyl. Hoping that steric hindrance at the

carbonyl group might favour the desired pathway, (49b) was oxidized under the same condition as (49a), but, as with (49a), there was no evidence for isoxazoline (129) formation, but only for the usual diacylhydroxylamine, (130b). Formation of (130a)

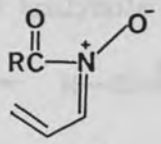


(130a)



(130b)

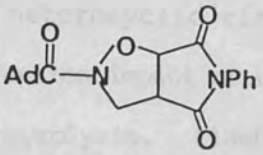
and (130b) seem to illustrate the extreme reactivity of the carbonyl group in N-acyl nitrones. However an alternative explanation may be due to the wrong configuration of N-acyl nitrone required for successful electrocyclization. This is based upon the fact that oxidation of N-allylhydroxamic acids (49a) or (49b) leads to their respective acyl nitroxide (characterized by e.s.r. spectra) which undergo 2nd order disproportionation reactions supposedly to acyl nitrone (128) and hydroxamic acid (for which rate constants have been measured - see Chapter 3). The alternative stereoisomer (131) might predominate, precluding isoxazoline formation.



(131)

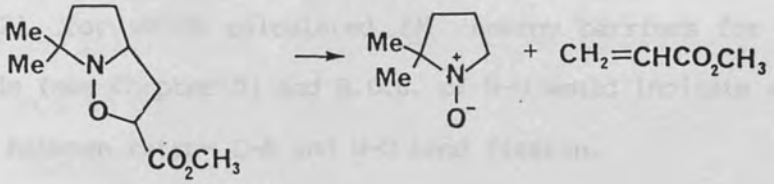
The failure of electrocyclization of the vinyl nitrone shows that a new approach to the trapping of acyl nitrones is required. Such an approach could be achieved by the generation of acyl nitrone in a non-nucleophilic environment, as represented by the retro-cycloaddition reaction of isoxazolidines in the

presence of scavengers.



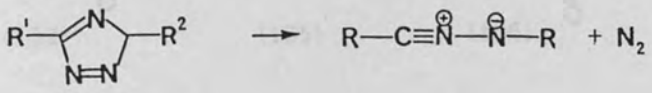
(132)

The attempted thermal retro- 1,3-dipolar cycloaddition of (132) in dichlorobenzene in the presence of benzyl alcohol at 110°C and 178°C, showed no presence of the nucleophile acylates. This is probably due to a not high enough temperature for successful retro- reaction. In contrast it is reported that the retro- 1,3-dipolar cycloadddition of monocyclic isoxazolidines (133) derived from nitrones and conjugated double bond systems undergo reaction under mild conditions.[125]



(133)

The retro- D-A of 2,5-diphenyltetrazole[125] (134) has an activation energy Ea = 32.4 kcal/mole and $\Delta S^{\neq} = -2.6$ cal $mol^{-1}k^{-1}$.



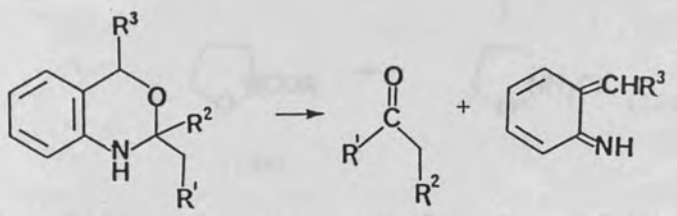
(134)

The calculated activation energies (see Chapter 5) for the retro- D-A of N-acylisoxazolidines (135) and (136) range between ca. 60-63 kcal/mole and ca. 58-61 kcal/mole respectively, this would indicate that thermal fragmentation of (137) and (132)

would require much higher temperatures than (134).

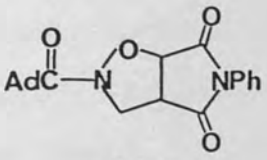
It is known that heterocyclic rings can undergo retro-cyclization following electron impact or ultraviolet irradiation, or by high temperature pyrolysis. Flash vacuum pyrolysis is a high thermal energy technique; for example, it was recently shown that flash pyrolysis at 750°C of dihydrobenzoxazines (137)[126] causes retro- D-A to give ketone and azaxylylene.

Work is in progress on the flash pyrolysis of (138)



(137)

and (132), for which calculated ΔH energy barriers for model compounds (see Chapter 5) and B.D.E. of N-O would indicate a fine balance between retro- D-A and N-O bond fission.



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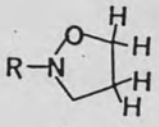

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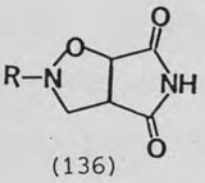

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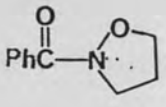
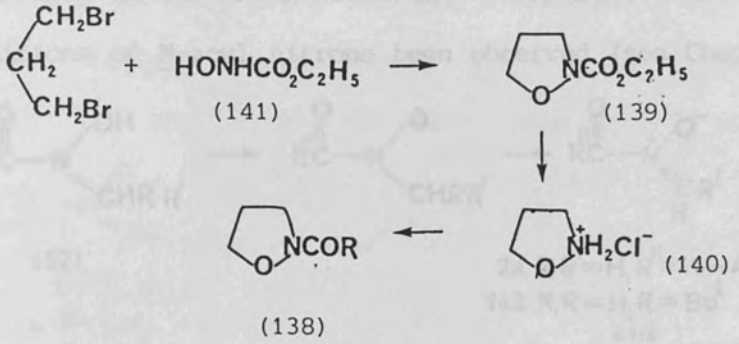


(138)

The preparation of (132) involves procedures outlined in Chapter 1.

Preparation of N-benzoylisoxazolidine (138) was first reported by King,[127] it involves the condensation of trimethylene bromide with N-hydroxyurethane to give 2-carbethoxyisoazolidine

(139). On boiling with dilute HCl, this is decarboxylated to give isoxazolidine hydrochloride (140) in 90% yield. Isoxazolidines are strong nucleophiles and undergo acylation with acid chlorides. A disadvantage of this method is the cost of the N-hydroxyurethane (141).

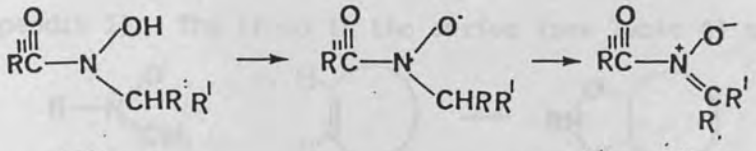


An alternative and cheaper method is reported by Johnson et al[69]. The preparation of (138) was achieved by the one-step reaction of trimethylene bromide and N-benzoylhydroxylamine in the presence of base followed by distillation of product under reduced pressure.

Chapter 5

Semi-empirical calculations on cycloaddition reactions

N-Acyl nitrones (2) are postulated as intermediates in the one-electron oxidation of N-alkylhydroxamic acids [see Chapter 1]. If such a species exists it should undergo 1,3-dipolar cycloaddition as do other nitrones. Only in two cases have cycloadditions of N-acyl nitrone been observed (see Chapter 4).



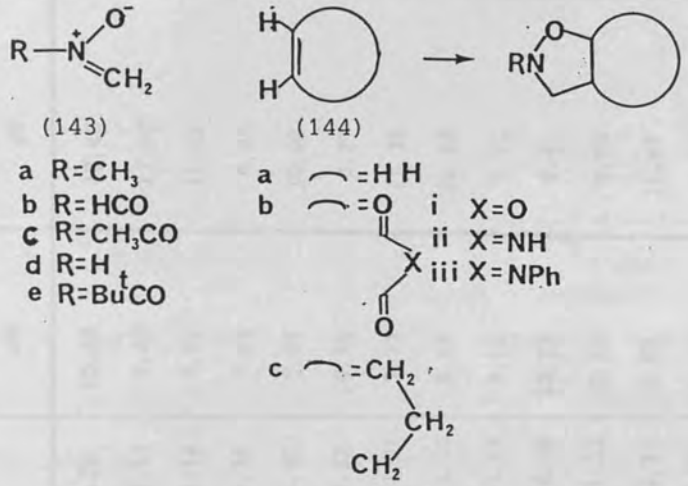
(52)

2a $R, R^{I}=H, R^{II}=1-Ad$

142 $R, R=H, R=Bu^{t}$

In both of these the electrophilic reactivity of the carbonyl carbon was reduced by the presence of a tertiary alkyl substituent (2a, 142). Qualitative considerations would suggest that in cycloaddition reactions the acyl nitrone might be expected to be more reactive than are other nitrones lacking the electron-withdrawing substituent. However, as described in Chapter 4, further attempts to intercept (2) in this way have failed. In order to evaluate whether the qualitative analysis was sound, a critical examination was undertaken using semi-empirical M.O. methods (MNDO and AM1) to investigate the energy profile for model cycloaddition reactions of nitrones with and without acyl substituents. A brief explanation of M.O. methods and the approximations used in solving M.O. electronic structure of complex molecules is given in Appendix I to this Chapter.

In the literature, studies of 1,3-dipolar and other cycloaddition reactions indicate that the frontier M.O's are important; the HOMO - LUMO interactions (see Chapter 4) are the major factor involved in determining whether such reactions are possible. Such a study was undertaken on a series of cycloadditions of (143) using the MNDO M.O. method, and results are shown in Table 4 [for details on mechanics of calculations see Appendix I]. The trend in the series (see Table 4) shows



that the HOMO - LUMO energy difference decreases as the electron-withdrawing character of the dienophile group increases. The major interaction is between the HOMO of the diene/dipole and the the LUMO of the dienophile/dipolarophile. The relationship between $E_{HOMO - LUMO}$ and kinetic rate of reactions has been reported by Sustmann et al (Fig. 18).[103,128] In the case of dipolar cycloaddition (Fig. 19), Sustmann reported that the rate ($\log k$) depends exponentially on $E_{HOMO - LUMO}$ (Fig. 18) and for 1,3-dipolar cycloadditions to a given dipole, a plot of $\log k$ against E_{HOMO} dipolarophile (Fig. 19) follows a parabola.

MNDO CALCULATIONS OF THE HOMO-LUMO ENERGY SEPARATION OF SELECTED 1,3-DIPOLAR CYCLOADDITION REACTIONS

	DIPOLE HOMO eV	DIPOLE LUMO eV	DIPOLAROPHILE HOMO eV	DIPOLAROPHILE LUMO eV	DIPOLE-DIPOLAROPHILE HOMO-LUMO eV	DIPOLARO-DIPOLE HOMO-LUMO eV
143a + 144a	-8.98	0.28	-10.18	1.32	10.30	10.46
143a + 144bi			-11.70	-1.51	7.47	11.98
143a + 144bii			-11.17	-1.16	7.82	11.45
143a + 144biii			-9.07	-1.14	7.84	9.35
143a + 144c			-9.72	0.98	9.96	10.00
143b + 144a	-9.24	-0.31	-10.18	1.32	10.56	9.87
143b + 144bi			-11.70	-1.51	7.73	11.39
143b + 144bii			-11.17	-1.16	8.08	10.86
143b + 144biii			-9.07	-1.14	8.10	8.76
143b + 144c			-9.72	0.98	10.22	9.41
143c + 144a	-9.18	-0.03	-10.18	1.32	10.50	9.90
143c + 144bi			-11.70	-1.51	7.67	11.42
143c + 144bii			-11.17	-1.16	8.01	10.89
143c + 144biii			-9.07	-1.14	8.04	8.79
143c + 144c			-9.72	0.98	10.16	9.44

TABLE 4

Another factor in such reactions involves the matching of the orbitals in diene/dipolarophile [reflected in the (co-efficient of atoms)^2] which determines the stereo- and regioselectivity of such reactions. In the reactions studied in this Chapter, the latter is not a factor as all dipolarophiles considered are symmetrical.

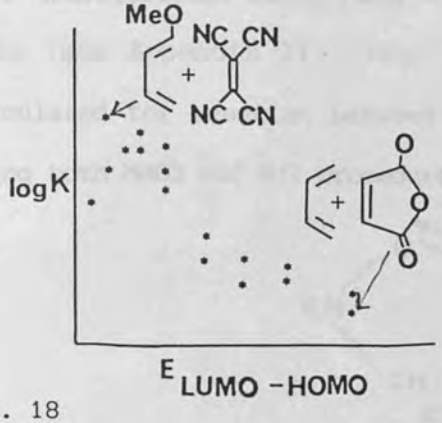


Fig. 18

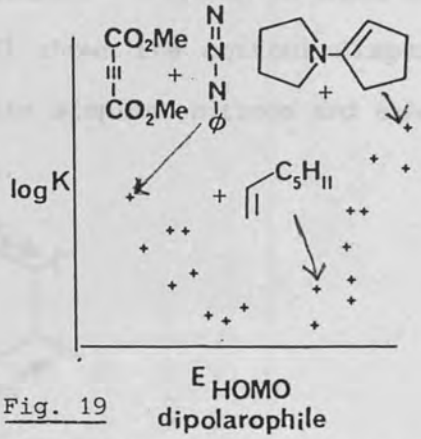


Fig. 19

As an extension to qualitative arguments based upon the HOMO - LUMO interactions, M.O. methods were used to investigate the energy profile for model cycloaddition reactions of nitrones including acyl nitrones to simple alkenes. The calculations were then extended to investigate the difference between the energetics of endo and exo approach of 1,3-dipoles to a carbonyl substituted alkenes and 1,3-dipole which exhibit steric effect with bulky substituents to such alkenes. For reasons detailed in Appendix I, these calculations used both MNDO and the more recently available AM1 approximations. The detailed procedure for the calculations is given in Appendix II.

MNDO and AM1 calculations were carried out using the AMPAC programme system. Two reaction co-ordinates were defined (Fig.

20), R_1, corresponding to cleavage of the C-C bond of the cycloadduct and R_2, corresponding to the cleavage of the C-O bond. Enthalpies of formation were calculated at fixed values of R_1 and R_2, with full optimization of the remaining 3N-8 degrees of freedom, and used to construct a contour diagram. All T.S's were characterized using FORCE constant[129] keyword in input data file (see Appendix II). Fig. 21 shows the contour diagrams calculated for reaction between the simplest nitrone and ethene using both MNDO and AM1 procedures.

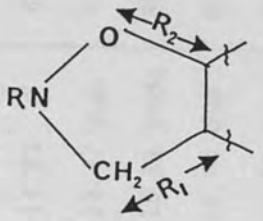
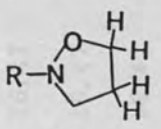


Fig. 20

The series of cycloadditions (Fig. 22) was devised to enable quantitative, as well as qualitative effects of steric and electronic factors on the activation energy of the cycloaddition and its reversal to be made.



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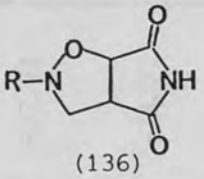


(136)

Fig. 22

Table 5 summaries the results from RHF AM1 calculations. The quantities listed are heats of formation (ΔH_f) for reactants, T.S. and products; the corresponding enthalpies of activation ($\Delta H^{\neq}$); the lengths (R_1, R_2) of forming C-X bonds in each T.S..

AM1 METHOD CALCULATIONS OF THE 1,3-DIPOLAR CYLOADDITION REACTIONS OF SELECTED SIMPLE NITRONE AND ACYL NITRONE WITH ETHENE OR MALEIMIDE

nitr	alkene	ΔH_f reactant	ΔH_f reactant	t.s	product	$\Delta H_f^{\neq}$	$\Delta H_r^{\neq}$	R^1	R^2
143d	144a	16.94	16.47	51.31	-8.48	17.90	59.79	2.148	2.035
143b	144a	-0.986	16.47	29.28	-31.18	13.79	60.46	2.159	2.093
143e	144a	-19.45	16.47	12.53	-50.10	14.83	62.63	2.158	2.086
143d	144bii	16.94	-33.71	-0.31	-59.09	16.47 exo	58.78 exo	2.180	2.015
				-1.67	-58.81	15.11 endo	58.14 endo	2.210	2.043
143b	144bii	-0.986	-33.71	-20.16	-80.24	14.54 exo	60.09 exo	2.108	2.101
				-21.16	-80.14	13.54 endo	58.98 endo	2.214	2.065
143e	144bii	-19.45	-33.71	-38.40	-99.40	14.76 exo	61.00 exo	2.166	2.065
				-37.27	-98.23	15.89 endo	60.96 endo	2.202	2.071

TABLE 5

For many years there have been arguments over whether or not Diels-Alder type reactions are concerted and synchronous. Whilst experimental results e.g. $\Delta S^{\neq}$,[130] $\Delta V^{\neq}$ [131] and kinetic isotope effects[132] support a concerted and synchronous mechanism Dewar et al[133] have argued mainly based upon semi-empirical M.O. calculations (RHF/UHF MINDO/3 and RHF/UHF MNDO) that in almost all Diels-Alder reactions formation of one bond between the reactants runs well ahead of that of the other. This implies appreciable biradical character for the transition state. The results of a number of ab initio calculations[134] with limited electron correlation on such systems on the other hand indicate that fully concerted and synchronous mechanisms are preferred. In these calculations closed-shell species (RHF) involved in the concerted processes and the open-shell (biradical) UHF species encountered in the non-concerted path can not be compared fairly, since these methods artificially favour one path over the other. Unlike the closed-shell RHF and open-shell UHF methods, the multiconfiguration SCF (MCSCF) calculations[135] enable comparison on the same energy scale.

Present MCSCF and higher level correlated calculations on representative 1,3-dipolar cycloadditions[135b] indicate that concerted pathway is favoured over the biradical path. Furthermore, unlike the biradical pathway, the predicted activation barriers for the concerted process lie in the correct experimental range.

From the calculations described in this chapter (see Fig.

ENERGY CONTOUR MAPS OF THE AM1 AND MNDO GRID CALCULATIONS OF THE REACTION OF SIMPLE NITRONE AND ETHENE

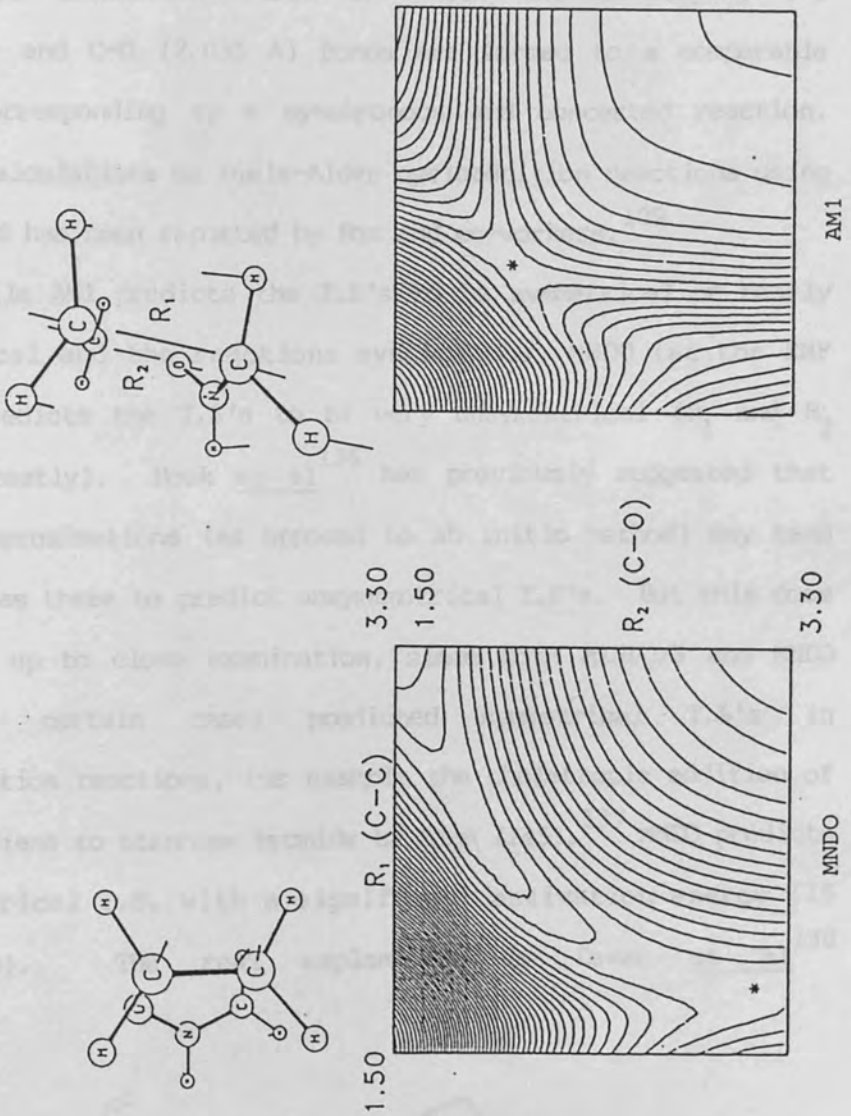
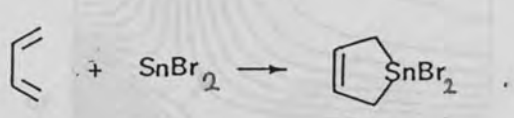


Fig. 21

21) on the reaction between $CH_2=\overset{+}{N}H\overset{-}{O}$ and ethene, it is apparent that the MNDO method leads to a transition state for cycloadddition in which bonding is strongly developed only along R_1 (C-C) co-ordinate corresponding to an asynchronous reaction. The result of the AM1 procedure (Fig. 21) leads to a much more symmetrical transition state in which the developing C-C (2.148 A) and C-O (2.035 A) bonds are formed to a comparable extent corresponding to a synchronous and concerted reaction. Similar calculations on Diels-Alder cycloaddition reactions using AM1 method has been reported by Fox and co-workers.[109]

While AM1 predicts the T.S's to be symmetrical or nearly symmetrical and the reactions synchronous, MNDO (at the RHF level) predicts the T.S's to be very unsymmetrical (R_1 and R_2 differ greatly). Houk et al[136] has previously suggested that Z.D.O. approximations (as opposed to ab initio method) may tend in cases as these to predict unsymmetrical T.S's. But this does not hold up to close examination, since both MINDO/3 and MNDO have in certain cases predicted symmetrical T.S's in cycloaddition reactions, for example the cheletropic addition of 1,3-butadiene to stannous bromide to form (145).[137] MNDO predicts a symmetrical T.S. with a significant activation energy (15 kcal/mole). The real explanation by Dewar et al[138]



(145)

DIFFERENCE ENERGY CONTOUR MAP OF THE AM1 AND MNDO METHODS FOR THE REACTION OF SIMPLE NITRONE AND ETHENE

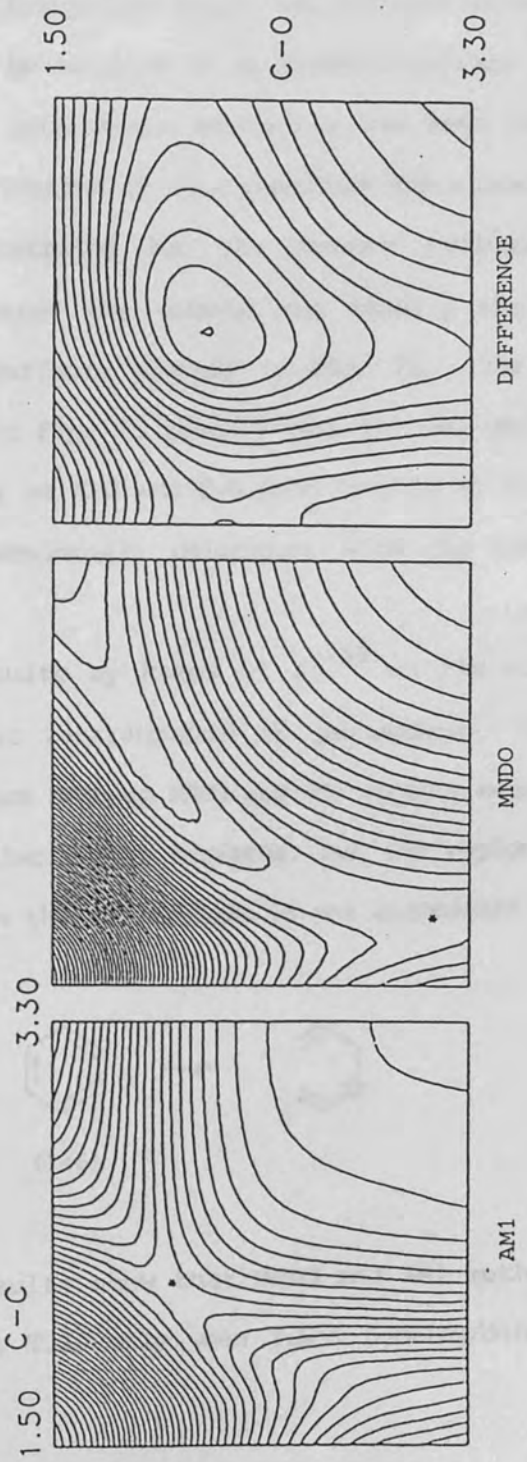


Fig. 23

lies on the well-known failing of MINDO/3 and MNDO in their tendency to overestimate repulsion interactions between atoms when the distance between them is 1.5-2.5 A; two such bonds occur in a cycloaddition transition state, and the cumulative effect is partially relieved by adoption of an asymmetricalized T.S.. This overestimation of interatomic repulsions has been corrected in AM1 by reparameterization of core repulsion functions. This has been nicely demonstrated for the nitrone cycloadditions by Rzepa,[139] who plotted the contour map showing the difference between the two surfaces plotted in Fig. 21. The difference surface, plotted in Fig. 23 reveals that the two methods differ the most in energy at C-C and C-O bond lengths of 2.3 and 2.1 A respectively, approximately coincident with the predicted AM1 T.S. (Fig. 23).

Further results by Rzepa et al[139] on the Claisen type [3, 3] sigmatropic rearrangement of pentadienal (146), again using the difference between MNDO and AM1 contour maps, once more reveal quite similar energy surfaces, but the region of maximum difference between the two methods is not coincident with either

(146)

T.S.. These results show that MNDO and AM1 methods predict totally different T.S. only when T.S's forming/deforming bonds

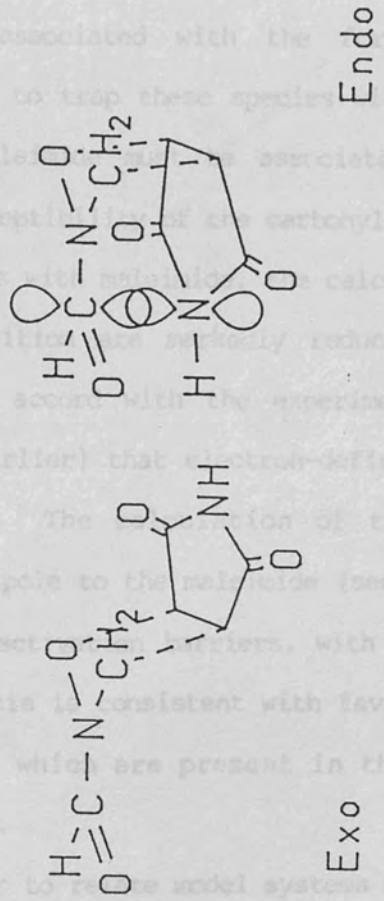


Fig. 24

are in the region 1.5-2.5 A and that asymmetry is not intrinsic in the MNDO method.

Table 5 gives calculated values of $\Delta H^{\neq}$ for selected nitrones with ethene or maleimide. Comparison of the calculated activation energies for the reaction of the model N-formyl nitrones with that of the N-H species using AM1 shows enhanced reactivity associated with the formyl derivatives. Evidently the failure to trap these species with dipolarophiles other than N-phenylmaleimide must be associated with the very high nucleophilic susceptibility of the carbonyl carbon.

For the reactions with maleimide, the calculated activation barriers for cycloaddition are markedly reduced compared with those for ethene, in accord with the experimental observation (see Chapter 4 and earlier) that electron-deficient alkenes are good dipolarophiles. The calculation of the exo and endo approach of the 1,3-dipole to the maleimide (see Table 5) showed small differences in activation barriers, with the endo pathway slightly favoured. This is consistent with favourable secondary orbital interactions which are present in the T.S. for endo addition (see Fig. 24).

Finally, in order to relate model systems more closely with experimental systems (2a) and (142) [see Chapter 4], calculations were extended to the reaction of the N-pivaloyl nitrone (143e) with ethene and maleimide (see Fig. 25). Comparison with the formyl system reveals negligible steric effect in the ethene reaction, but for the reaction with maleimide the exo/endo

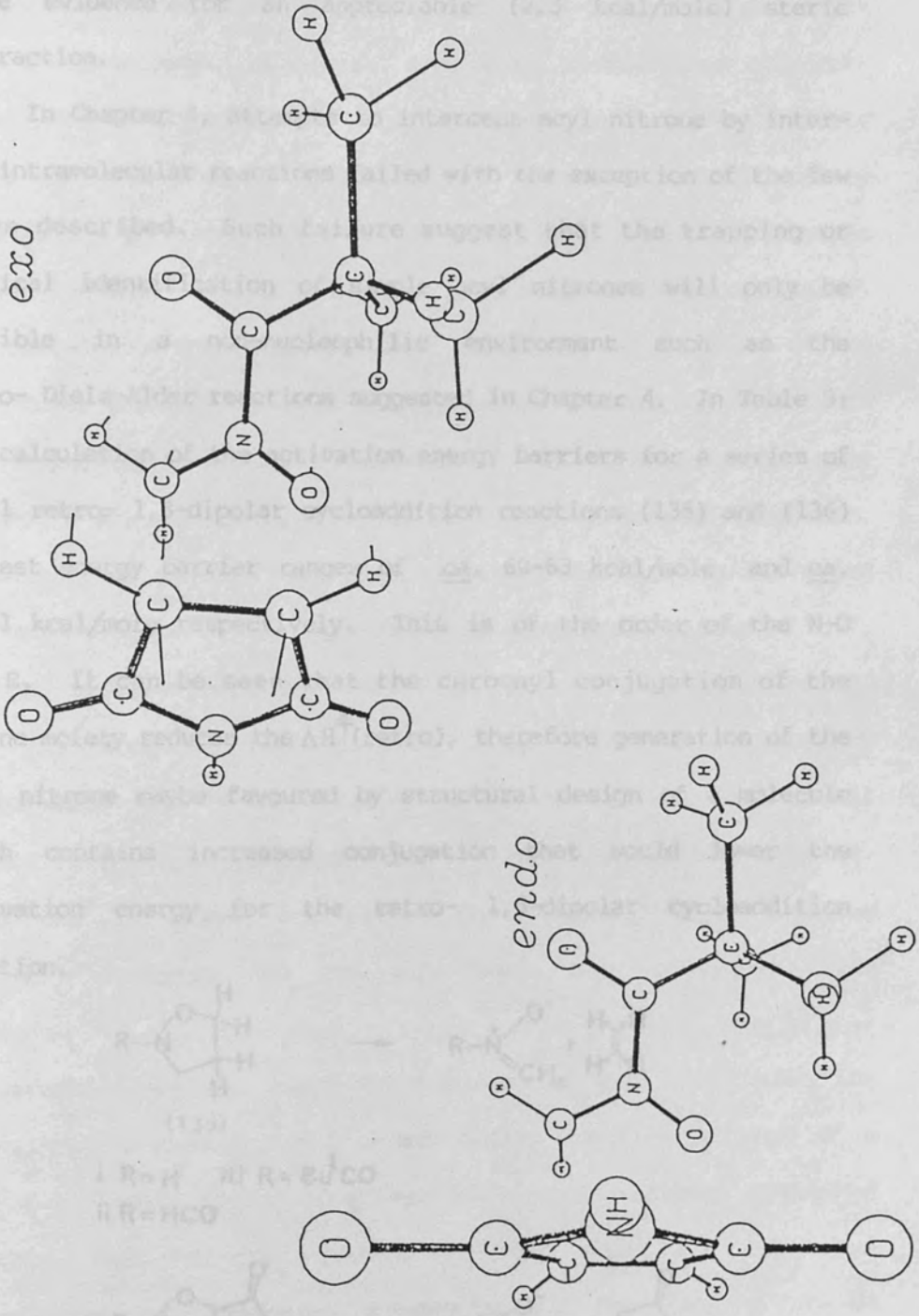


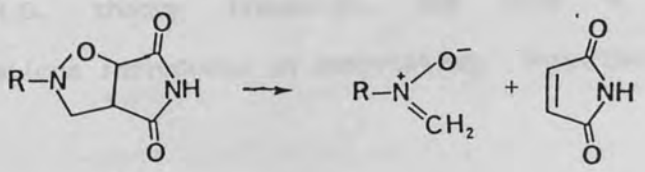
Fig. 25

preference is reversed. In this case, for the exo-approach the steric effect is again negligible; only for the endo-approach is there evidence for an appreciable (2.3 kcal/mole) steric interaction.

In Chapter 4, attempts to intercept acyl nitrone by inter- and intramolecular reactions failed with the exception of the few cases described. Such failure suggest that the trapping or physical identification of simple acyl nitrones will only be possible in a non-nucleophilic environment such as the retro- Diels-Alder reactions suggested in Chapter 4. In Table 5; the calculation of the activation energy barriers for a series of model retro- 1,3-dipolar cycloaddition reactions (135) and (136) suggest energy barrier ranges of ca. 60-63 kcal/mole and ca. 58-61 kcal/mole respectively. This is of the order of the N-O B.D.E. It can be seen that the carbonyl conjugation of the alkene moiety reduces the $\Delta H^{\neq}$(retro), therefore generation of the acyl nitrone maybe favoured by structural design of a molecule which contains increased conjugation that would lower the activation energy for the retro- 1,3-dipolar cycloaddition reaction.

(135)

i R=H iii R= Bu^tCO
ii R=HCO



(136)

APPENDIX I

Introduction: An Outline of Semi-Empirical M.O. Methods

The pioneering work of Schroedinger, Heisenberg and Dirac led the development of several approaches to molecular calculation. Eventually molecular orbital theory proved its versatility over other methods of calculation. Molecular orbital theory provides a precise description of molecular electronic structure only for one-electron molecules; for many electron molecules, approximations are required. Full analytical calculations of the molecular orbitals for most many-electrons systems may be reduced to a purely mathematical probelm.[140] The solutions to these probelms are now possible due to the advent of digital computers. However, the computer time required, even for diatomic molecules is considerable. On the otherhand, many applications of M.O. theory requires only qualitative or semi-quantitative knowledge of the form of the molecular from which the neccessary information can be extracted. Approximation molecular orbital theories can be approached from two basically different views. The two approaches are called the Huckel[141] (and extexted Huckel[142]) theory and the approximate self-consistent field theory.[143] In both theories the π-electrons of the planar unsaturated organic molecules are treated explicitly with the remaining σ-electrons and atomic nuclei consider as part of a non-polarizable core. They are based upon a scheme developed within M.O. theory framework, but with a number of simplifications introduced in computation. Experimental data on

atoms or prototype molecular systems are used to estimate values for quantities entering the calculations as parameters. Hence these simplified techniques are referred to as semi-empirical methods.

The self-consistent field (SCF) methods can be applied to molecules with molecular weight up to 1200. The general SCF M.O. method, the various approximations involved, and all the integrals required have been reviewed by Parr.[144] It is in the area of the semi-empirical choices for integrals that the various semi-empirical methods differ. The semi-empirical methods estimate at least some of the integrals from empirical data at the sametime reducing the number of integrals which must be computered on the Cray, different levels of ab initio M.O. calculations (in which no or very little empirical data is used) have become possible on small and medium size molecules, although computer time is still considerable and its uses as a tool, comparable to the various spectroscopic techniques which are avaliable to organic chemists, are still limited.

Review of avaliable semi-empirical methods

(i) CNDO- Complete neglect of differential overlap

This is the most elementary theory in which electron repulsions are included in calculation as opposed to Huckel type calculation. The Pople group proposed CNDO[145] and its variation CNDO/2[145] which satisfy the transformation invariance which simplifies the full M.O. theory calculations. The inner shell electrons are treated as a rigid core and only valence electrons are treated explicitly. Complete neglect of differential overlap

means that $\phi_\mu\phi_\nu$ integral, where ϕ_μ and ϕ_ν are assumed to be two different atomic orbitals, always vanishes, whether the orbitals μ and ν are centred on the same atom or on different atoms. Obviously this will simplify considerably the calculations, all two-centre overlap integrals will vanish. Many of the coulomb and electron repulsion integrals will vanish.

The approximations made in the CNDO method means that all atomic states for a given configuration have the same energy.

(2) INDO- intermediate neglect of differential overlap[146,147]

The CNDO approximation introduces electron-electron repulsion in the simplest form. Adequate allowances are not made different interactions between electrons with parallel or anti-parallel spins, particularly if they are on the same atom. As a result, CNDO calculations frequently are unable to give an account of the separation of states arising from the same configuration. Therefore CNDO, when applied to radicals, does not lead to any spin density in σ-orbitals as do the full unrestricted calculation. In the INDO method, also proposed by the Pople group,[146] it applies the zero differential overlap approximation in all electron interaction (repulsion and attraction) integrals except those involving one centre exchange integral only i.e. $(\phi_\mu\phi_\nu|\ \phi_\mu\phi_\nu) = 0$ (μ and ν are on the same atom). This means that all one centre exchange integrals like $(p_x p_y | p_x p_y)$ are retained. These are important since they introduce quantitatively the effect of Hund's rule, according to which electrons in different atomic orbitals on the same atom

will have a lower repulsion energy if their spin are parallel.

(3) MINDO- Modified intermediate neglect of differential overlap

Dewar and Baird[148] introduced three modifications onto the original INDO method with the specific aim of calculating heats of formation. Dewar and Baird in this case sought to best fit experimental data, whereas Pople tried to reproduce the results by using the same basis set but reducing approximation. These approaches have been updated and are called MINDO/2[149] and MINDO/3.[150]

(4) NDDO- Neglect of diatomic differential overlap

This method of calculation was proposed by Pople, Santry, and Segal.[145] Of the three levels of approximation considered, it is the closest to the full SCF equation of Roothan.[151] The NDDO method still applies the Z.D.O. approximation for orbitals situated on different atomic centres, but retains integrals including the product of the two orbitals on the same atom. In other words two-centre coulomb integrals of the type $(\phi_\mu\phi_\nu|\phi_\lambda\phi_\sigma)$, where orbitals μ and ν come from atom A and λ and σ from atom B, are retained. In addition, one-centre coulomb and exchange integrals involving up to four different orbitals on the same atom may occur. Retaining monoatomic differential overlap removes the restrictions that the two-centre integrals be independent of orbital type.

(5) MNDO- Modified neglect of diatomic differential overlap

The Dewar group[152] introduced experimental data in parameterization of certain integrals in the NDDO procedure as seen in the MINDO method, allowing their solution to be sought. In the INDO method, on which MINDO is based, two-centre electron-electron repulsion and core-electron attractions are spherically averaged, whereas in the NDDO method they show angular dependance due to possible different orientations of the higher multipole.

In the MNDO method, the two-centre repulsion integrals are solved by parameterization with empirical data as opposed to the analytical solution in the NDDO method. In MNDO E_{AB} (Eq. 7) is found by empirical parameterization.

$$E_{TOT} = E_{el} + E_{AB\ repulsion}$$

Eq. 7

(6) AM1 method- Austin model 1

The treatment of core-electron attraction (Eq. 8) and core-core repulsions (Eq. 9) in MNDO are as follows.

$$V_{\mu\ \nu_e} = -Z_B(\mu_\nu^{A\,A}, s^B s^B) + f_2(R_{AB})$$

Eq. 8

$$E_{AB}^{core} = Z_A Z_B(s^A s^A, s^B s^B) + f_3(R_{AB})$$

Eq. 9

Overestimation of repulsion interactions occurs in the MNDO when distances between atoms are at ca. their van der Waals distances apart. The AM1 method is a reparameterization of the MNDO

method, in which the core repulsion functions (CRF) [Eq. 10] are modified. Dewar et al[153] modified the existing functions by additional Gaussian terms. In the AM1 method the CRF are as follows.

$$CRF\ (AB) = Z_A Z_B\ _{ss}\ [\ 1 + F(A) + F(B)] \qquad \text{Eq. 10}$$

Where $F(A) = \exp\ (-\alpha_A R_{AB}) + K_{Ai} \exp\ [\ L_{Ai}\ (R_{AB} - M_{Ai})^2]$

$F(B) = \exp\ (\ \alpha_B R_{AB}) + K_{Bi} \exp\ [\ L_{Bi}\ (R_{AB} - M_{Bi})^2]$

M and K are parameters

Two strategies were used to modify CRF and reduce interatomic repulsions at large separations. In the first, one or more attractive Gaussians were added to compensate the excessive repulsions in MNDO (referring to Eq. 8, 9). In the second, repulsion Gaussians were centred at smaller interatomic separations, leading to an overall reduction of the main term in the expression (Eq. 10) for the core repulsions and hence reducing repulsions at larger interatomic distances.

In the case of C, H, and N both type of gaussians were used. In oxygen only repulsive Gaussians were used. These improvements have led to better calculations of hydrogen bonding strengths and hydrogen-bond lengths, and also to more realistic transition state energies and geometries.

RHF (restricted) and UHF (unrestricted) Hartree-Fock theories

In INDO and NDDO methods, treatment for closed-shell

molecules (paired electrons) and open-shell molecules (unpaired electrons) differ. For closed-shell molecules the RHF (restrictive Hartree-Fock) theory is used,[154] in which it limits the electrons to a pairwise occupation of the molecular orbitals, i.e. orbitals of the molecule are either doubly occupied or empty.

In INDO, the directionality of chemical bonding is only represented in the resonance integrals $\beta_{\mu\lambda}$ while in NDDO it is also included in the two-centre electron-electron repulsions and core-electron attractions. Therefore NDDO methods are expected to be superior to an INDO based method whenever directionality effects play an important role in a molecule.

Choice of semi-empirical methods used

The MINDO/3 method performs very well on hydrocarbons but probelms arise in the case of molecules containing heteroatoms, due to neglect of one-centre overlap in the underlying INDO approximation on which MINDO/3 is based: integrals describing the dipole fields due to lone-pair electrons in hybrid A.O's are neglected. As a result dipole-dipole repulsions in compounds such as hydrazine are neglected and their calculated ΔH_f values are too negative. Therefore MNDO and AM1 calculations were used in this work.

The calculations used were carried out by using standard MNDO and AM1 procedures as implemented in the MOPAC and AMPAC programs (avaliable from the Quantum Chemistry Program Exchange (QCPE)) using the VAX FPS-164 system at Imperial College and the

Cray machine at U.L.C.C. (for details on mechanics of calculation see Appendix II). Transition states were located approximately by Grid calculation of simple systems. Refinement was achieved by minimization of the norm of gradient, and characterized by calculating force constants (Hessian) matrix.[129]

APPENDIX II

PROCEDURE FOR M.O CALCULATIONS

Keywords in AMPAC PROGRAM

1 SCF- one self consistent field calculation; used when a single geometry is to be studied, usually to test Z-matrix.

AM1- Austin Model 1; Dewar new reparameterized method of MNDO.

Bond- Final bond order matrix to be printed.

Charge = n- Charge on system = n (e.g. NH_4^+ = charge = 1).

Density- Final density matrix to be printed.

E.S.R- RHF unpaired spin density to be calculated.

Excited- First excited singlet to be calculated.

FORCE- Force calculation specified.

GEO-OK- Override interatomic distances check.

MINDO/3- The MINDO/3 hamiltonian to be used.

NLLSQ- SCF optimizing gradient function for locating transition state.

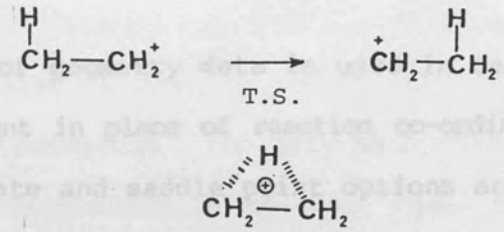
PRECISE- Criteria to be increased by 100 times.

PULAY- PULAY's optimizing function to be used in SCF calculation.

SADDLE- Transition state in a simple chemical reaction is to be optimized. After the first geometry specifying the reactant, and any symmetry functions have been defined, the second geometry specifying the products is defined using the same format as that of the first geometry. Can only be used in cases such as Eq. 11

in which one bond is formed as one is broken e.g.

H-migration.



Eq. 11

STEP1 = n- Step size for first co-ordinate in GRID calculation.

STEP2 = n- Step size for second co-ordinate in GRID calculation.

SYMMETRY- Symmetry conditions to be imposed.

T = nnn- Time of nnn seconds requested (note space!).

THERMO- A thermodynamic calculation is to be performed.

TRIPLET- Triplet state required.

UHF- Unrestricted Hartree-Fock calculation, RHF calculation is default of no UHF keyword.

Data file for AMPAC jobs on VAX FPS-164 at Imperial college.

Line 1	line of keywords
Line 2	first title line
Line 3	second title line
Line 4 + n	geometric data n = 0, 1, 2, ...
Line 4 + (n + 1)	symmetry data, if required
Line 4 + (n + 3)	reaction co-ordinate data, if required
OR Line 4 + (n + 3)	second set of geometry data, if required

Second set of geometry data is used in saddle point calculations (present in place of reaction co-ordinate data). Reaction co-ordinate and saddle point options are mutually exclusive. If no symmetry data required reaction co-ordinate follows first geometric data (as line 4 + (n + 1)). Order of keywords are not important, but abbreviations should be avoided.

Geometrical specifications (Z-matrix) - input

The geometry can be defined in terms of either internal or cartesian co-ordinates (internal co-ordinates preferred).

Internal co-ordinates

For any one atom (i) this consists of an interatomic distance in angstroms from an already-defined atom (j), an interatomic angle in degrees between atom i and j and an already defined atom (k), (k and j must be different atoms), and finally a torsional angle in degrees between atom i, j, k and an already defined atom l (l can not be the same as k or j).

Atom 1 has no co-ordinates at all and is referred to as

the origin. Atom 2 must be connected to atom 1 by an interatomic distance only. Atom 3 can be connected to atom 1 or 2, and must make and angle with atom 2 or 1 (thus 3-2-1 or 3-1-2); no dihedral is possible for atom 3. By default, atom 3 is connected to atom 2.

Constraints

(i) Interatomic distances must be greater than zero. Zero Angstroms is not acceptable. The only exception is if the parameter is symmetry-related to another atom, and is the dependant function.

(ii) Angles must be positive. This constraint is for the benefit of the user only as negative angles are the result of errors in the construction of the geometry.

(iii) Dihedral angles can normally only assume definable angles. If atom i makes a dihedral with j, k, and l and the three atoms j, k, and l are in a straight line, then the dihedral has no definable angle. During the calculation this constraint is checked continuously, and if atom j, k, and l lie within 0.1 Angstroms of a straight line the calculation will output an error message and then stop. In such cases dummy atoms can be incorporated to relieve this situation. Dummy atoms (99 or XX) are used in the definition of the geometry and are deleted automatically from any cartesian co-ordinate geometry files. Dummy atoms are purely mathematical points.

Z-matrices are used as input data files into AMPAC sytem, each internal co-ordinate is followed by an integer, to indicate

action to be taken.

No 1 means to optimize the internal co-ordinate;

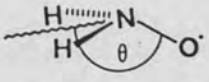
No 0 means do not optimize the internal co-ordinate;

No -1 means reaction co-ordinate or grid index.

Only one reaction co-ordinate is allowed in a data file, but this can be made more versatile by the use of symmetry. The values of the reaction co-ordinate should be followed immediately after the geometry data and any symmetry data (After geometry data if no symmetry data present). In AMPAC system free-format type input is acceptable.

If two reaction co-ordinate are required, then AMPAC assumes that the two-dimensional space in the region of the supplied geometry is to be mapped. The two-dimensions to be mapped are in the plane defined by the (-1) labels. Step sizes in the two directions are supplied by using STEP 1 and STEP 2 on the keyword line (Grid calculation). An 11 by 11 grid data point output file results from these calculations, the central data point in the grid being the initial data point in the Z-matrix.

An example below (150) explains the Z-matrix more clearly, including most keywords.



(150)

Input data file (Z-matrix) for (150).

```
AM1 UHF BONDS SYMMETRY
NITRIC OXIDE
VARIATION OF ANGLE  θ
XX 1.00
XX 1.00 0
N  1.00 0 90 0
O  1.22 1 90 -1   0 1  3 2 1
H  1.08 1 90  1  90 0  3 2 1
H  1.08 0 90  0 -90 0  3 2 1

5 1 6
5 2 6

100 120 140 160 180 200 220 240 260 280 300
```

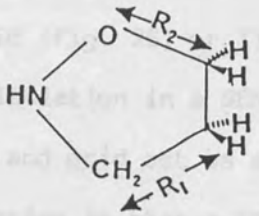
NB. 5 1 6 means that bond length between 5 and 3, and 6 and 3 are equal.

5 2 6 means bond angle between 5, 3 and 2, and 6, 3, and 2 are equal.

Z-matrix for (135i).

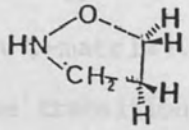
```
AM1
NITRONECYCLOADDUCT
USED IN GRID CALCULATIONS
H
N 1.01 1
C 1.47 1 109.00 1
H 1.12 1 110.00 1   15.00 1  3 2 1
H 1.12 1 110.00 1  175.00 1  3 2 1
C 1.53 1 105.00 1 -105.00 1  3 2 1
C 1.53 1 105.00 1  -25.00 1  6 3 2
O 1.45 1 105.00 1    0.00 1  7 6 3
H 1.12 1 110.00 1  100.00 1  6 3 2
H 1.12 1 110.00 1 -150.00 1  6 3 2
H 1.12 1 110.00 1  100.00 1  7 6 3
H 1.12 1 110.00 1 -100.00 1  7 6 3
```

Z-Matrix for grid calculation of (135i).




```
AM1 STEP1=0.20 STEP2=0.20 T=300M GEO-OK
AM1 NITRONE/ETHENE REACTION
GRID EXAMPLE
H
N 1.018 1
C 1.363 1  116.11 1
H 1.100 1  118.33 1  18.35 1  3 2 1
H 1.103 1  117.44 1  168.7 1  3 2 1
C 2.100 -1  96.17 1  -98.3 1  3 2 1
C 1.370 1  101.16 1  -25.0 1  6 3 2
O 2.000 -1 102.29 1    3.7 1  7 6 3
H 1.098 1   95.24 1   97.7 1  6 3 2
H 1.098 1   95.24 1 -146.8 1  6 3 2
H 1.098 1  121.54 1  100.6 1  7 6 3
H 1.098 1  121.54 1  -92.6 1  7 6 3
```

Z-Matrix for locating transition state of (135i).




```
AM1 T=240M NLLSQ FORCE
AM1 NITRONE/ETHENE REACTION
LOCATING TRANSITION STATE
H
N 1.018 1
C 1.363 1 116.11 1
H 1.100 1 118.33 1   8.35 1  3 2 1
H 1.103 1 117.44 1 168.74 1  3 2 1
C 2.100 1  96.17 1 -98.33 1  3 2 1
C 1.378 1 101.16 1 -25.04 1  6 3 2
O 2.000 1 102.29 1   3.74 1  7 6 3
H 1.098 1  95.24 1  97.73 1  6 3 2
H 1.098 1  92.68 1 146.80 1  6 3 2
H 1.098 1 121.54 1 100.65 1  7 6 3
H 1.098 1 121.41 1 -92.66 1  7 6 3
```

Notes

A grid (Fig. 26) of 11 by 11 points is printed out at the end of calculation in a SENDIC.DAT file in which case the file is edited and grid act as a data file for the contour package. An alternative is that a SENDIC.DAT file is initiated in which case, the data file is ready as input file for contour drawing package using the Cyber 855 computer at Imperial College.

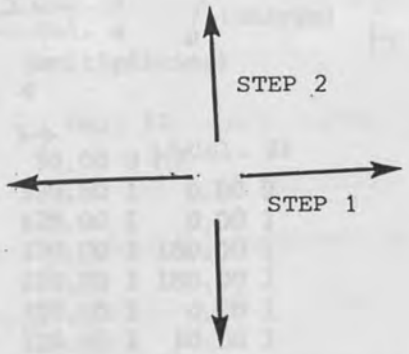


Fig. 26

Approximate transition states are located by inspection of the global energy surface in terms of value of R_1 and R_2 (see calculation Z-matrix). These are used as values in a new Z-matrix (see transition state Z-matrix); these values are then refined and all other bond lengths and angles are optimized. The calculation of force constant matrix locates a transition state (not necessarily the global T.S.), but global T.S. can be located by judicious choice of initial R_1 and R_2. When the force matrix is diagonalized, a T.S. is located if and only if one cartesian co-ordinate is negative (if more than one, the stationary point is not a T.S. but rather an intermediate).

<u>Input data file for Cray MOPAC system</u>

In the MOPAC system free-format type input is unacceptable, data must be inputed in format.

A typical example is shown below:-

```
JOB,US=UHCA016,JN=MALEII1,MFL=300000,T=100.
ACCESS,DN=MNDO,ID=KZCCHEM.
MNDO
/EOF
MNDO                          Col. 22
   Col. 1  Col. 2                          Col. 33-34
                              (charge)
0 0          Col. 4          0             |-> DATE, NAME OF FILE
99          (multiplicity)
99 |->Col. 4
1  1.10 0    |-> Col. 12
7  1.21 1    90.00 0 |->Col. 21
6  1.47 1   120.00 1    0.00 0             3 2 1
8  1.20 1   120.00 1    0.00 1             4 3 2
6  1.44 1   120.00 1  180.00 1             4 3 2
6  1.36 1   120.00 1  180.00 1             6 4 5
6  1.44 1   120.00 1    0.00 1             7 6 4
8  1.20 1   120.00 1   10.00 1             8 3 2
1  1.10 1   120.00 1  180.00 1             6 4 3
1  1.10 1   120.00 1  180.00 1             7 6 4
0 0 0 0 0 0 0 0 0 0
99
/EOF                       10 zero's to complete geometry data
```

Data files for reaction co-ordinates can be done using MOPAC systems and general information is avaliable from ULCC booklet.

<u>NB</u>. Dummy atoms in MOPAC on cray computer is represented as 99.

Operating instructions

The keywords for computation on the Cray computer is shown below. Filenames are written in the form; FILENAME.Cry;n.

```
SENDIC /TARGET=CRAY /STYLE=FILE
```

On completion of computation, output files are returned from the Cray as an ULCC.JTMP.LOG;n file. Output files in MOPAC system contain calculation of eigenvectors (energy of electronic levels), orbital co-efficients, atomic charges, and optimized geometries (i.e. internal and cartesian co-ordinates).

MOPAC system does not contain the AM1 hamiltonian option, grid calculations, calculation of thermodynamic quantities and force constant required for accurate location of transition states (these are avaliable in AMPAC system).

Chapter 6

Experimental

(i) Infra-red (IR) spectra were recorded on a Perkin-Elmer FT 1710 fourier transform spectrometer. Samples were examined between sodium chloride plates either as nujol (solid) or as neat films (liquids).

(ii) Proton magnetic resonance (^{1}H-n.m.r.) spectra

The ^{1}H-n.m.r. spectra for most sample were recorded on a Jeol FX 90Q (90MHz) n.m.r. spectrometer. Frequently samples were also recorded on a Hitachi Perkin-Elmer R-24 (60MHz) high resolution n.m.r. spectrometer or on a 200MHz Nicolet NT200 Instrument Model. Infrequently samples were recorded on a Bruker WH 400 pulse FT n.m.r. spectrometer.

Deuteriochloroform ($CDCl_3$) solutions were doped with tetramethylsilane (TMS) to provide an internal standard and the chemical shifts are expressed as -parts per million from this standard.

(iii) Carbon nuclear magnetic resonance (^{13}C-n.m.r.)

The ^{13}C-n.m.r. spectra were recorded on a Jeol FX 90Q (90MHz) and Nicolet NT200 (200MHz) n.m.r. spectrometers. $CDCl_3$ and TMS were used as a solvent and standard respectively.

(iv) ^{1}H/^{13}C- 2D correlation and Attached Proton Test experiments were recorded on a Bruker AM 400 (400MHz) by Dr. C. Szantay at the Chemistry dept., University of Leeds.

(v) Electron spin resonance (e.s.r.) spectra

Electron spin resonance spectra were recorded on a Varian

E-4 e.s.r. spectrometer operating at a frequency of approximately 8.98 GHz (x-band): resonance absorptions were centred at magnetic field strengths of 3270 Gauss (G). Modulation amplitudes and scan times were varied to obtain maximum resolution.

Spectra were recorded using quartz tubes of 3 mm diameter. Solutions were carefully deoxygenated by bubbling with a capillary flow of oxygen-free nitrogen for ca. 3 minutes immediately prior to e.s.r. examination. Sample tubes were sealed with gas tight push-on caps to permit prolonged spectral running time.

Hyperfine coupling constants were determined from the recorded derivative spectra and are quoted in units of Gauss. The values were corrected by a factor of 0.977 for a field scan error on the particular spectrometer used.

(vi) Melting-points

Melting points (mpt.) were determined in open capillary tubes using an Electrothermal melting-point apparatus with range selection guide. All values are uncorrected.

(vii) Cleaning of glassware

All glassware for e.s.r. spectroscopy, n.m.r. spectroscopy and liquid chromotagraphy was cleaned with chromic acid as follows: the glassware was immersed in chromic acid and allowed to soak overnight. After removal of chromic acid and washing with distilled water, the glassware was soaked in 2M H_2SO_4. The glassware was then thoroughly washed with distilled water and allowed to air dry in oven.

(viii) Elemental analysis

Elemental analyses were carried out by Mrs. L. Whitaker in the chemistry department. All analyical samples were dried in the presence of P_2O_5 *in vacuo*.

(ix) Chromatography

Thin-layer chromatography was done using pre-made Merck silica gel GF_{254} (type 60) plates. The thickness of the ordinary t.l.c. plates was 0.25 mm. Preparative thick layer chromatography plates were prepared using Merck silica gel GF_{254} (type 60). The thickness of the p.t.l.c. plates was 1 mm. Unless otherwise stated, air dried plates were developed with ethyl acetate/pet. ether 40-60 25 : 75 and visualized beneath a UV lamp and/or iodine staining. Kieselger 60 (mesh 230-400 mesh ASTM) was used for flash chromatography.

Experiments

1. Preparation of O-Benzoyl-N-t-butylhydroxylamine

$$Bu^tNH_2 \longrightarrow Bu^tNHOC(=O)Ph$$

O-Benzoyl-N-t-butylhydoxylamine was prepared from commercial t-butylamine by the reaction with dry dibenzoyl peroxide according to a modification of Zinner's method.[72]

(a) Dibenzoyl peroxide

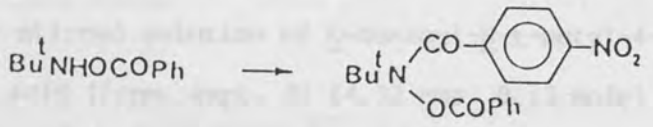
Commercial dibenzoyl peroxide (paste with 30% water by weight) (30 gms, 0.12 mole) in chloroform (200 cm^3) was added slowly and with stirring into excess methanol (300 cm^3). The precipitate, dibenzoyl peroxide freed from water, was filtered and dried in air (19.5 gms, 0.08 mole).

(b) Freshly distilled t-butylamine (16.5 gms, 0.158 mole) was added with stirring to a solution of freshly recrystallized dibenzoyl peroxide (17.3 gms, 0.07 mole) in sodium dried benzene (150 cm^3). The reaction was stirred for one hour at 40°C. Additional t-butylamine (12.5 cm^3, 0.12 mole) was then added and stirring continued for 48 hours at 40°C. Chloroform (100 cm^3) was added to cooled reaction mixture and the precipitated amine salt was filtered and washed with chloroform (2 x 50 cm^3). The filtrate was washed with acidic iron(II)sulphate solution (60.0 gms/ $FeSO_4.7H_2O$, 110 cm^3/ H_2O, 6 cm^3/ H_2SO_4). The organic layer was dried ($MgSO_4$), filtered, and evaporated to give an amber oil (8.63 gms, 64% based on dibenzoyl peroxide).

IR (ν cm^{-1}, neat): 3225 (N-H str.), 3091-3025 (C-H aromatic str.), 1719 (CO str.), 1602 (C=C str.).

^{1}H nmr (δ ppm, $CDCl_3$): 1.21 (s, 9H, Bu^t), 7.3-8.2 (m, 5H, Ar-H).

2. Preparation of N-4-nitrobenzoyl-N-t-butyl-O-benzoylhydroxylamine.

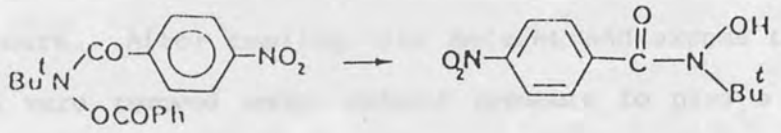


To a stirred solution of crude O-benzoyl-N-t-butylhydroxylamine (4.0 gms, 0.021 mole) (from expt. 1) in sodium dried benzene (50 cm^3) was added sodium hydroxide dried pyridine (1.66 gms, 0.021 mole) and 4-nitrobenzoyl chloride (3.93 gms, 0.021 mole). A slight precipitate of pyridinium hydrochloride resulted. The mixture was refluxed for 8 hours cooled and poured into 2M HCl (150 cm^3). The solution was extracted with chloroform (250 cm^3). The organic phase was washed with 2M HCl (2 x 50 cm^3), then water (2 x 50 cm^3), then dried ($MgSO_4$) and filtered. Evaporation of solvent by rotary evaporation yielded a white crystalline product. Recrystallization from CH_2Cl_2/hexane gave the title compound as colourless crystals (4.52 gms, 62%), mpt. 98-100°C (lit. mpt.[83] 98-99°C).

IR (ν cm^{-1}, nujol): 1760 (OCO C=O str.), 1640 (NCO C=O str.), 1605 and 1580 (C=C str.).

^{1}H-nmr (δ ppm, $CDCl_3$): 1.6 (s, 9H, Bu^t), 7.2-7.9 (m, 9H, Ar-H).

3. Preparation of N-t-butyl-4-nitrobenzohydroxamic acid



Hydrazine hydrate (5.79 gms, 0.10 mole, 7.5 mol.eguiv.) was added to a stirred solution of O-benzoyl-N-t-butyl-4-nitrobenzohydroxamic acid (from expt. 2) (4.52 gms, 0.13 mole) in absolute ethanol (30 cm^3). The reaction mixture was stirred at 40°C for 1 1/2 hours, cooled and poured on to ice/water (200 cm^3). Then put in fridge for two hours. The resulting solid was filtered off and dried in a desiccator over NaOH pellets. Recrystallization from CH_2Cl_2/hexane gave the title compound as needles (2.14 gms, 0.009 mole), mpt. 113-114°C (lit. mpt.[83] 113°C).

IR (ν cm^{-1}, nujol): 3548-2545 br. (3150 max. OH str.), 1620 (max. C=O str.)

^{1}H-nmr (δ ppm, $CDCl_3$): 1.32 (s, 9H, Bu^t), 7.1-7.4 (m, 5H, Ar-H).

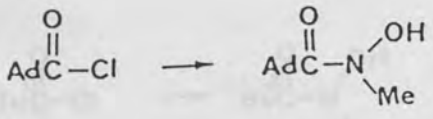
4. Preparation of 1-adamantanecarboxylic acid chloride

To a stirred suspension of 1-adamantanecarboxylic acid (14.6 gms, 0.115 mole) in sodium dried toluene (20 cm^3) was added dropwise to a solution of oxalyl chloride (10 gms, 0.056 mole) in toluene (50 cm^3). When

the initial violet reaction had subsided the mixture was refluxed for 4 hours. After cooling, the solvent and excess oxalyl chloride were removed under reduced pressure to give a white crystalline product. Recrystallization from sodium dried ether gave colourless crystals (10.3 gms, 93%), mpt. 49-51°C (lit. mpt.,[155] Aldrich 48°C).

IR (ν cm^{-1}, nujol): 1780 (max. C=O str.).

5. Preparation of N-methyl-N-(1-adamantanecarbonyl)hydroxylamine.



To a suspension of N-methylhydroxylamine hydrochloride (Aldrich, 4.176 gms, 0.5 mole) in CH_2Cl_2 (100 cm^3, pretreated with anhydrous K_2CO_3 to remove acidic impurities), was added potassium carbonate (6.90 gms, 0.05 mole).

The mixture was stirred at room temperature for 20 mins. To this solution was then added 1-adamantanecarboxylic acid chloride (from expt. 4) (9.94 gms, 0.05 mole) in methylene chloride (50 cm^3), dropwise over a period of 15 mins. The reaction mixture was further stirred for three hours at room temperature and followed by t.l.c.. The inorganic residue was separated and washed with CH_2Cl_2 (10 cm^3) and the combined organic layer (ether, methylene chloride) was washed with 2M HCl (4 x 50 cm^3) and water (10 cm^3) and dried over Na_2SO_4. Removal of the solvent

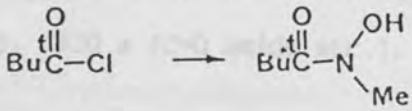
under reduced pressure resulted in an oil (8.00 gms) which, when chilled with hexane/acetone - CO_2 ice bath) gave desired hydroxamic acid. Recrystallization from hexane/CH_2Cl_2 gave a white crystalline solid (6.45 gms, 66%), mpt. 134-136°C (lit. mpt.[64] 139°C).

IR (ν cm^{-1}, nujol): 3225-3075 br. (OH str.), 1582 (C=O str.)

^{1}H-nmr (δ ppm, $CDCl_3$): 1.60-1.95 (two s, 15H, 1-adamantyl), 3.4 (s, 3H, -N-CH_3), 9.1 (br.s, 1H, N-OH).

Elemental analysis: Found C, 68.7; H, 9.3; N, 6.7%. $C_{12}H_{19}NO_2$ requires C, 68.9; H, 9.2; N, 6.7%.

6. Preparation of N-methyl-N-pivaloylhydroxylamine.



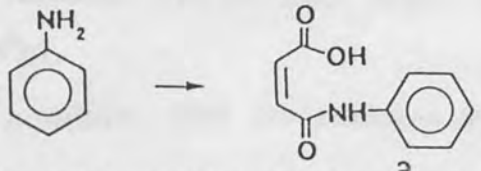
The title compound was prepared using a procedure similar to the preparation of N-methyl-N-(1-adamantanecarbonyl)hydroxylamine (expt. 5). The crude reaction product was purified by column chromatography (SiO_2, ethyl acetate/methylene chloride 50 : 50) to give colourless crystalline solid, (1.02 gms, 16%), mpt. 67-68°C (lit. mpt.[64] 67-68°C).

IR (ν cm^{-1}, nujol): 3100max.(OH str.), 1620 (C=O str.)

^{1}H-nmr (δ ppm,$CDCl_3$): 0.6 (s, 9H, Bu^t), 1.65 (s, 3H, N-CH_3), 4.55 (s, 1H, N-OH).

Elemental analysis: Found C, 54.96; H, 9.92; N, 10.68%. $C_6H_{13}NO_2$ requires C, 54.97; H, 10.09; N, 10.64%.

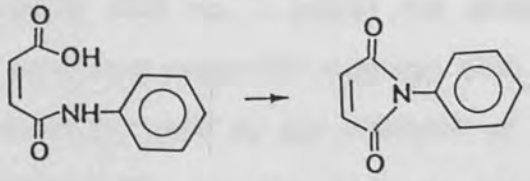
7. Preparation of maleanilic acid.[156]



Reagent grade aniline (36.4 cm^3, 0.391 mole) in diethyl ether (200 cm^3) was added in aliquots to a stirred solution of maleic anhydride (39.2 gms, 0.400 mole) in diethyl ether (500 cm^3). The resulting thick suspension was refluxed at room temperature for one hour. After cooling to 15-20°C, followed by filtration, a cream-coloured powder resulted, (72.1 gms, 0.378 mole, 97%), mpt. 196-198°C (lit. mpt.[156] 201-202°C).

IR (ν cm^{-1}, nujol): 3450 (two N-H strs.), 1695 max. (C=O carboxylic str.), 1620 s (C=O amide str.).

8. Preparation of N-phenylmaleimide.[156]



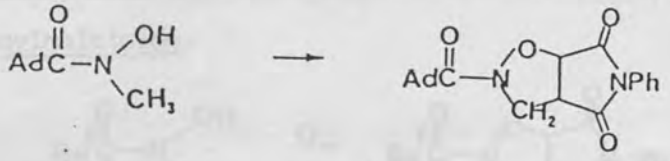
To a suspension of acetic anhydride (145 gms, 1.42 moles) and anhydrous sodium acetate (13 gms, 0.159 mole) was added crude maleanilic acid (63.2 gms, 0.33 mole) from expt. 7, and the resulting suspension was dissolved by swirling and heating on a steam bath for 30 mins (sodium acetate fails to dissolve completely). After cooling to room temperature, the mixture was poured into ice/water (260 cm^3). The resulting yellow precipitate was filtered OFF and residue washed with ice-cold water

(3 x 500 cm^3) and once with a portion of pet. ether 40-60 (500 cm^3). Recrystallization from cyclohexane gives canary-yellow crystalline needles, (29.11 gms, 51%), mpt. 87.5-89°C (lit mpt.[156] 88-89°C).

IR (ν cm^{-1}, nujol): 3050 (CH aromatic str.), 1705 max. (C=O str.).

^{1}H-nmr (δ ppm, $CDCl_3$): 6.83 (s, 2H, vinyl hydrogens), 7.19-7.60 (m, 5H, Ar-H).

9. Oxidation of N-methyl-N-(1-adamantanecarbonyl)hydroxylamine in the presence of N-phenylmaleimide.



N-Methyl-N-(1-adamantanecarbonyl)hydroxylamine (209 mg, 1 mmole) was dissolved in methylene chloride (30 cm^3) and N-phenylmaleimide (173 mg, 1 mmole) was added, the mixture was stirred and anhydrous magnesium sulphate (200 mg, used as drying agent) was added followed by the addition of silver oxide (240 mg, 1.04 mmole); the reaction mixture was stirred for 4 1/2 hours; upon completion of the reaction, the inorganic residue was filtered off and the methylene chloride removed under reduced pressure, to give an oil which solidified upon standing. Recrystallization from CH_2Cl_2/hexane gave a white powder, (310 mg, 82%), mpt. 187-188°C (lit. mpt.[64] 188°C).

IR (ν cm^{-1}, nujol): 1724 (-C(O)-N-C(O)- str.), 1640 (-C(O)-N-O- str.)

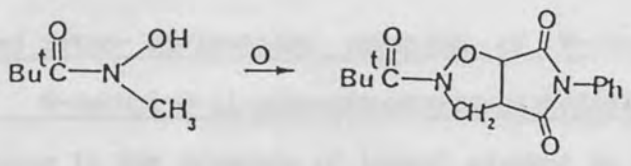
^{1}H-nmr (δ ppm, $CDCl_3$): 1.50-2.10 (m, 15H, adamantyl protons), 3.68-3.82 (m, 2H, -C-N-CH-CH), 4.40-4.55 (d, 1H, -C-N-CH-CH), 5.05-5.20 (d, 1H, -C(O)-CH-O-N-), 7.15-7.60 (m, 5H, Ar-H).

For more detail on n.m.r. spectroscopic experiments see Chapter 4.

Elemental analysis: Found C, 68.85; H, 6.40; N, 7.22%. $C_{22}H_{24}N_2O_4$ requires C, 69.5; H, 6.3; N, 7.4%.

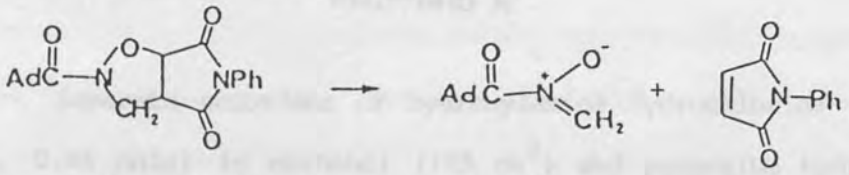
Mass spectrum (FAB), (m/z, 8 eV Xe),: 413 ($M^+ + Na^+$), 385, 381 ($M^+ + H^+$).

10. Oxidation of N-methyl-N-pivaloylhydroxylamine in the presence of N-phenylmaleimide.



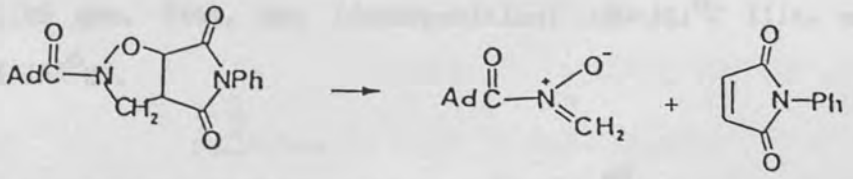
Oxidation of N-methyl-N-pivaloylhydroxylamine was done under similar conditions as that of N-methyl-N-(1-adamantanecarbonyl-hydroxylamine (expt. 9). A t.l.c study of reaction products (SiO_2, CH_2Cl_2) showed the major component to be N-phenyl-maleimide. A 200MHz n.m.r. spectrum of crude reaction products showed traces of a compound with identical spectral pattern for isoxazolidine ring as the cycloadduct formed by oxidation of N-methyl-N-(1-adamantanecarbonyl)hydroxylamine in the presence of N-phenylmaleimide (expt. 9). Attempted separation of the compound using preparative t.l.c. on silica gel failed.

11. Attempted retro- Diels-Alder reaction of cycloadduct of N-methyl-N-(1-adamantanecarbonyl)hydroxylamine in chlorobenzene at 130°C.



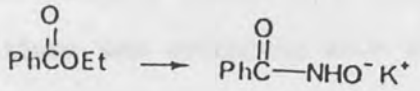
The N-phenylmaleimide adduct of title compound (22 mg, 0.058 mmole) was dissolved in chlorobenzene (2 cm^3), and benzyl alcohol (5.23 gms, 48.4 mmole) was added, and the mixture was heated on an oil bath for 18 hours at 132°C. The reaction mixture showed, on t.l.c. analysis, the presence of starting reagents; there was no evidence of formation of benzyl adamantanecarboxylate.

12. Attempted retro- Diels-Alder reaction of N-phenylmaleimide adduct of N-methyl-N-(1-adamantanecarbonyl)hydroxylamine in dichlorobenzene in the presence of benzyl alcohol at 180°C.



The title compound (22 mg, 0.058 mmole) was dissolved in dichlorobenzene (2 cm^3) with benzyl alcohol (5.23 gms, 48.4mmole) and was placed in a glass tube which was sealed, and heated for 18 hours in a Carius furnace at 179-180°C. The reaction mixture showed spots on t.l.c. consistent with starting materials; there was no evidence of acylation of benzyl alcohol.

13. Preparation of potassium benzohydroxamate.[157]



Separate solutions of hydroxylamine hydrochloride (31.14 gms, 0.44 mole) in methanol (173 cm^3) and potassium hydroxide (37.54 gms, 0.66 mole) in methanol (150 cm^3) were prepared at the boiling point of the solvent. Both solutions were cooled to 30-40^{o}C and alkali solution was added to the hydroxylamine with shaking. After all alkali solution has been added, the mixture is allowed to stand at 0^{o}C for 5 mins. Ethyl benzoate (90.76 gms, 0.66 mole) was then added to the mixture with shaking and the mixture was filtered immediately. The filtrate was stoppered and allowed to stand for 3 days at room temperature. The resulting precipitate was filtered, washed with methanol (10 cm^3), and allowed to dry. A white crystalline solid resulted, (25.99 gms, 34%), mpt (decomposition) 160-161^{o}C (lit. mpt.[157] 161-162^{o}C).

14. Preparation of 2-benzoylisoxazolidine.[69]

To a stirred solution of the above hydroxamate (14.7 gms, 0.084 mole) and anhydrous potassium carbonate (23.2 gms) in methanol (62 cm^3) and water (42 cm^3) was added 1,3-dibromopropane (18.7 gms, 0.092 mole) and the mixture was heated at 38^{o}C for 3

days. Evaporation of solvent under reduced pressure, resulted in a dark brown residue. Water (100 cm^3) was added to the residue and the mixture was extracted with ether (2 x 100 cm^3). The combined organic layer was dried ($MgSO_4$) and the ether evaporated under reduced pressure. The crude product was distilled under vacuum to give a colourless viscous liquid (5.12 gms, 35%), bpt 113-120°C at 0.1 mmHg (lit. bpt.[69] 124-126°C at 0.16 mmHg).

IR ($\nu\ cm^{-1}$, neat): 3060 (CH aromatic str.), 2964-2883 (CH aliphatic str.), 1631 max. (C=O str.), 1600 (C=C aromatic str.).

^{1}H-nmr (δ ppm, $CDCl_3$): 1.95-2.25 (quint, 2H, $-CH_2-\underline{CH_2}-CH_2-$), 3.65-3.93 (t, 4H, $\underline{CH_2}-N-\underline{CH_2}$), 7.10-8.10 (m, 5H, Ar-H).

Elemental analysis: Found C, 67.56; H, 6.24; N, 6.92%. $C_{10}H_{11}NO_2$ requires C, 67.78; H, 6.26; N, 6.90%.

Mass spectrum (m/z, 35eV): 177 (M^+, 2.95%), 161 (1.1%), 106 (7.98%), 105 (base peak, $PhCO^+$).

15. Preparation of N,O-dibenzoylhydroxylamine.

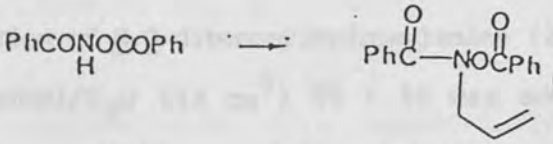
To a suspension of potassium benzohydroxamate (8.00 gms, 0.046 mole) in dioxane (50 cm^3) was added benzoyl chloride (6.42 gms, 0.046 mole) with constant stirring. The reaction mixture was then boiled for 5 mins, cooled to room temperature and solution was poured into distilled water (800 cm^3). The resulting precipitate was filtered and washed with methanol.

Recrystallization from 95% ethanol gave a white crystalline solid (9.33 gms, 84%), mpt. (decomposition) 158-160°C (lit. mpt.[69] 161-162°C).

IR(ν cm^{-1}, nujol): 3150 (N-H str.), 1764 s (max. C=O carboxylate str.), 1640 s (max. C=O amide str.), 1600 (C=C aromatic str.).

^{1}H-nmr (δ ppm, acetone-d_6): 7.75-8.65 (m, 10H, Ar-H).

16. Attempted N-allylation of N-benzoyl-O-benzoylhydroxylamine using KOH as base.

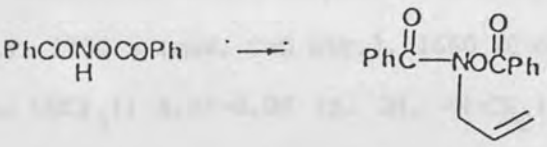


To a suspension of N,O-dibenzoylhydroxylamine (2 gms, 8.29 mmoles) in dioxane/ethanol (50 cm^3) 50 : 50 at 10°C was added KOH (0.47 gms, 8.29 mmole) in ethanol (14 cm^3). The reaction mixture was shaken vigorously, and then allowed to stand for 5-10 mins at ice-bath temperature, after which the salt was filtered off and washed with a little ethanol (10 cm^3) and finally ether (25 cm^3). The solid was dissolved in sodium hydride dried dimethoxyethane (DME); followed by the addition of allyl bromide (4.51 gms, 4.5 mole equiv.) and refluxed for 3 hours. A solid precipitated from the DME which was filtered and gave a yellow/cream powder (1.13 gms, 64%), mpt. 230-234°C. Infra-red the of solid showed unfamilar stretching not characteristic of N-alkylated hydroxylamine esters but consistent with that of 1,3-diphenylurea (carabanilide) (lit. mpt.[155] 234-236°C).

IR (ν cm^{-1}, nujol): 3327-3275 (two peaks, N-H str.), 1643 s (max. C=O str.), no ester carbonyl peak around 1750's.

^{1}H-nmr (δ ppm, acetone-d_6): 6.60-7.6 (m, 10H, Ar-H), 7.65-8.30 (br. s, 2H, NH-C(O)-NH).

17. Allylation of N,O dibenzoylhydroxylamine using K_2CO_3 as the base.



To a solution of N,O-dibenzoylhydroxylamine (2.62 gms, 0.011 mole) in methanol/H_2O (13 cm^3) 50 : 50 was added anhydrous potassium carbonate (2.17 gms, 0.16 mole) the initial very exothermic reaction was controlled by cooling with ice-bath. After reaction was complete allyl bromide (1.92 gms, 0.016 mole) was added and stirred at 42°C for one day. After this time, water (45.5 cm^3) was added to the reaction mixture and extracted with chloroform (2 x 4.5 cm^3). The combined chloroform extracts were washed with water (3 x 22.5 cm^3), then dried with Na_2SO_4 then filtered. Evaporation of solvent at reduced pressure resulted in an amber oil. T.l.c. (SiO_2, ethyl acetate/pet. ether 60-80 40 : 60) indicated two major components. Separation of these was achieved by medium pressure liquid chromatography (SiO_2, ethyl acetate/pet. ether 60-80 20 : 80). Spectroscopic evidence shows that the compounds have similar n.m.r. characteristics.

(More polar)

IR (ν cm^{-1}, neat): 3050 (CH aromatic str.), 2925-2895 (CH

aliphatic str.), 1750 s (max. C=O str.), 1660 s (max. C=N (oxime) or C=O str.).

^{1}H-nmr (δ ppm, $CDCl_3$): 4.44-4.77 (d, 2H, -N-$\underline{CH}_2$), 5.14-5.70 (d, 2H, -CH=$\underline{CH}_2$), 5.77-6.54 (m, 1H, -$\underline{CH}$=CH_2), 7.27-8.45 (m, 10H, Ar-H).

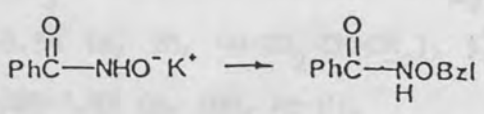
(Less polar)

IR (ν cm^{-1}, neat): 3050 (CH aromatic str.), 2925-2894 (CH aliphatic str.), 1750 s (max. C=O str.), 1660 (C=N or C=O str.).

^{1}H-nmr (δ ppm, $CDCl_3$): 4.84-5.05 (d, 2H, -N-$\underline{CH}_2$), 5.25-5.75 (d, 2H, -CH=$\underline{CH}_2$), 5.87-6.55 (m, 1H, -$\underline{CH}$=CH_2), 7.37-8.57 (m, 10H, Ar-H).

It was not possible from this spectral information to differentiate between N-allyl and O-allyl isomers.

18. Preparation of N-benzoyl-O-benzylhydroxylamine.

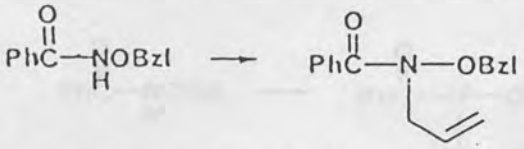


Using a procedure similar to the preparation of N-benzoyl--O-benzoylhydroxylamine (expt. 15), the title compound was prepared, (6.40 gms, 37%). Recrystallization from CH_2Cl_2/pet. ether 60-80 gave white crystalline solid, mpt. 102-103°C. (lit. mpt.[158] 103-105°C).

IR(ν cm^{-1}, nujol): 3140 (NH str.), 1641 s (C=O amide str.).

^{1}H-nmr (δ ppm, $CDCl_3$): 5.00 (s, 2H, -O-$\underline{CH}_2$-), 7.10-7.90 (m, 10H, Ar-H), 8.85 (br. s, 1H, -$\underline{NH}$-).

19. Preparation of N-allyl-N-benzoyl-O-benzylhydroxylamine



Using a procedure similar to the preparation of N-allyl-N-benzoyl-O-benzoylhydroxylamine (expt. 15) a crude amber oil resulted (340 mg, 58%). Separation of the title compound was by medium pressure liquid chromatography (SiO_2, ethyl acetate/ pet. ether 60-80 30 : 70) which gave two components. The more polar N-allyl-N-benzoyl-O-benzylhydroxylamine (140 mg, 24%) and the less polar allyl benzhydroximic benzoate (200 mg, 34%).

More polar: N-allyl isomer

IR (ν cm^{-1}, neat): 3050-3025 (CH aromatic str.), 2925-2850 (CH aliphatic str.), 1640 s (max. C=O amide str.), 1600 (C=C str.).

^{1}H-nmr (δ ppm, $CDCl_3$): 4.20-4.45 (d, 2H, -N-C<u>H</u>$_2$-), 4.65 (s, 2H, -N-O-C<u>H</u>$_2$-), 5.05-5.54 (m, 2H, -N-CH_2-CH=C<u>H</u>$_2$), 5.55-6.25 (m, 1H, -N-CH_2-C<u>H</u>=CH_2), 6.85-7.95 (m, 10H, Ar-H).

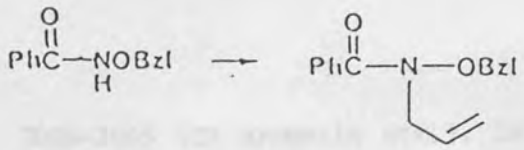
Less polar: O-allyl isomer

IR (cm^{-1}, neat): 3050-3025 (CH aromatic str.), 2925-2850 (CH aliphatic str.), 1640 s (max. C=N str.).

^{1}H-nmr (δ ppm, $CDCl_3$): 4.60-4.90 (d, 2H, -N-CH_2-), 5.13 (s, 2H, -O-CH_2-), 5.05-5.50 (dd, 2H, -O-CH_2-CH=C<u>H</u>$_2$), 5.70-6.40 (m, 1H, -O-CH_2-C<u>H</u>=CH_2), 6.90-7.90 (m, 10H, Ar-H).

N.m.r. interpretation is by comparison with model compounds in ref (69).

20. Preparation of N-allyl-N-benzoyl-O-benzylhydroxylamine using phase transfer catalyst tetrabutylammonium hydrosulphate.



To a suspension of N-benzoyl-O-benzylhydroxylamine (1.47 gms, 6.5 mmole) and tetrabutylammonium hydrosulphate (0.55 gms, 1.62 mmole) in benzene (16 cm^3) was added to potassium carbonate (1.47 gms, 0.0065 mole) in water (2 cm^3) followed by intensive shaking for 25 mins, until a thick slush is formed. Allyl bromide (0.780 gms, 0.0065 mole) was then added and the mixture was heated to 60-70°C and reaction followed by t.l.c. until starting material had disappeared. After completion of reaction, the organic phase was extracted with 2M HCl to remove basic material, washed until neutral with aqueous sodium sulphate, filtered, and the solvent was removed. An amber oil resulted (150 mg, 9%). Separation by L.C. (SiO_2, ethyl acetate/pet. ether 40-60 30 : 70) gave N-allyl compound (20 mg, 1.17%) and O-allyl isomers (21 mg, 1.24%).

N-allyl compound

IR (ν cm^{-1}, neat): 3065-3032 (CH aromatic str.), 2927-2880 (CH aliphatic str.), 1642 s (C=O amide str.), 1602 (C=C aromatic str.).

^{1}H-nmr(δ ppm, $CDCl_3$): 4.29-4.31 (d, 2H, -N-CH_2-), 4.62 (s, 2H,

-N-O-$\underline{CH_2}$), 5.14-5.42 (m, 2H, -N-CH_2-CH=$\underline{CH_2}$), 5.74-6.12 (m, 1H, -N-CH_2-$\underline{CH}$=CH_2), 6.99-7.69 (m, 10H, Ar-H).

O-allyl isomers

IR (ν cm^{-1}, neat): 3086-3065 (CH aromatic str.), 2927-2874 (CH aliphatic str.), 1612s (C=N str.).

^{1}H-nmr (δ ppm, $CDCl_3$): 4.75-4.90 (d, 2H, -O-$\underline{CH_2}$-CH=CH_2), 5.18 (s, 2H, -N-O-$\underline{CH_2}$-), 5.30-5.43 (dd, 2H, -O-CH_2-CH=$\underline{CH_2}$), 5.83-6.35 (m, 1H, -O-CH_2-$\underline{CH}$=CH_2), 7.20-7.84 (m, 10H, Ar-H).

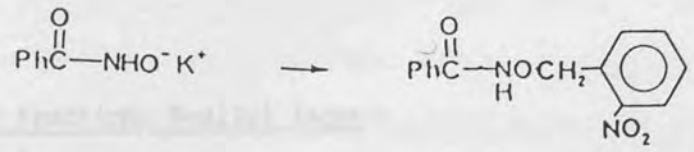
21. Preparation of benzohydroxamic acid.

A suspension of potassium benzohydroxamate (7.37 gms, 0.042 mole) in 1.25N acetic acid (34 cm^3) was stirred and heated until a clear solution was obtained. The solution was allowed to cool to room temperature, a white solid precipitated. The crystals which separated was washed with a little benzene and allowed to air dry (3.64gms, 63%), mpt. 125-127^{o}C (lit. mpt.[159] 126-130^{o}C).

IR (ν cm^{-1}, nujol): 3426 br (OH str.), 3295 s (NH str.), 1646 s (C=O amide str.).

^{1}H-nmr (δ ppm, acetone-D_6): 7.30-7.95 (m, 5H, Ar-H), no OH or NH chemical shifts.

22. Preparation of N-benzoyl-O-2-nitrobenzylhydroxylamine.



The title compound was prepared using a procedure similar to the preparation of N-benzoyl-O-benzoylhydroxylamine (expt. 15). Recrystallization from CH_2Cl_2/pet. ether 60-80 gave N-benzoyl-O--2-nitrobenzylhydroxylamine as a white crystalline solid (sensitive to direct sunlight) (6.34 gms, 40%), mpt. 111-112°C.

IR (ν cm^{-1}, nujol): 3145 (NH str.), 1640 s (C=O amide str.).

^{1}H-nmr (δ ppm, $CDCl_3$): 5.55 (s, 2H, -N-O-CH_2-), 7.26-8.25 (m, 9H, Ar-H), 9.13 (br. s, 1H, -NH-).

Elemental analysis: Found C, 61.83; H, 4.40; N, 10.26%. $C_{14}H_{12}N_2O_4$ requires C, 61.77; H, 4.41; N, 10.29%.

23. Preparation of N-allyl-N-benzoyl-O-2-nitrobenzylhydroxylamine

The title compound was prepared using a procedure similar to the preparation of N-allyl-N-benzoyl-O-benzylhydroxylamine (expt. 19). An amber viscous oil resulted (550 mg, 81%). Separation by medium pressure L.C. (SiO_2, ethyl acetate/pet.ether 60-80 flow rate 12 cm^3/min) gave two main components. The more polar fraction gave N-allyl-N-benzoyl-O-benzylhydroxylamine as a

pale amber oil (190 mg, 28%) and the less polar fraction gave allyl benzhydroximic 2-nitrobenzoate as a pale amber oil (90 mg, 13%).

More polar fraction: N-allyl isomer

IR (ν cm^{-1}, neat): 3084 (CH aromatic str.), 2926-2859 (CH aliphatic str.), 1651 s (C=O amide str.), 1603 (C=C aromatic str.).

^{1}H-nmr (δ ppm, $CDCl_3$): 4.20-4.35 (d, 2H, -N-C$\underline{H}_2$-), 4.65 (s, 2H, -N-O-C$\underline{H}_2$-), 5.14-5.42 (m, 2H, -N-CH_2-CH=C$\underline{H}_2$-), 5.74-6.12 (m, 1H, -N-CH_2-C$\underline{H}$=CH_2), 7.20-8.30 (m, 9H, Ar-H).

Less polar fraction: O-allyl isomer

IR (ν cm^{-1}, neat): 3082 (CH aromatic str.), 2928-2857 (CH aliphatic str.), 1614 s (C=N str.).

^{1}H-nmr (δ ppm, $CDCl_3$): 4.75-4.90 (d, 2H, -O-C$\underline{H}_2$-), 5.18 (s, 2H, -N-O-C$\underline{H}_2$-), 5.30-5.43 (d, 2H, -O-CH_2-CH=C$\underline{H}_2$), 5.84-6.35 (m, 1H, -O-CH_2-C$\underline{H}$=CH_2), 7.20-8.30 (m, 9H, Ar-H).

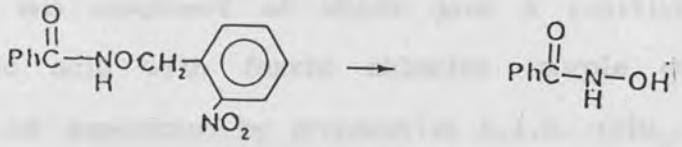
Elemental analysis: Found C, 65.42; H, 5.10; N, 8.99%. $C_{17}H_{16}N_2O_4$ requires C, 65.39; H, 5.13; N, 8.97%.

24. Preparation of N-allyl-N-benzoyl-O-2-nitrobenzylhydroxylamine using phase transfer catalyst triethylbenzylammonium hydrosulphate.

Using a procedure similar to the preparation of N-allyl--N-benzoyl-O-benzyl (expt. 20) using a phase transfer catalyst. An amber viscous oil resulted (1.29 gms, 96%). Separation by L.C. using same conditions as expt. 23 gave N-allyl compound as a pale amber oil (273 mg, 20%) and O-allyl isomers as a pale amber oil (70 mg, 5.2%).

IR, and ^{1}H-n.m.r. spectra are given in expt. 23

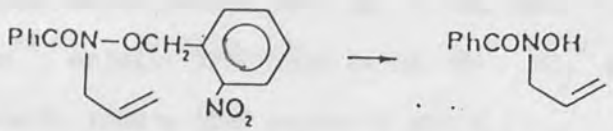
25. Photolysis of N-benzoyl-O-2-nitrobenzylhydroxylamine.



N-Benzoyl-O-2-nitrobenzylhydroxylamine, prepared in expt. 22 was dissolved in CCl_4 and placed in standard apparatus for photolysis. A medium pressure Hg lamp (UV > 320 nm) was used and placed in a pyrex-walled jacket. The pyrex filter is important since UV >320 nm leads to side-reactions.

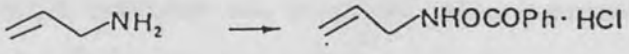
The reaction mixture was irradiated for 15-20 mins, the reaction followed by t.l.c. (SiO_2, CH_2Cl_2). The clear solution turned brown after irradiation for 15 mins. T.l.c. of reaction products (SiO_2, ethyl acetate/pet.ether 60-80) showed three major products, one gave a purple colouration with ferric chloride, indicative of hydroxamic acid. This product had the same Rf as authentic benzohydroxamic acid (expt. 21). IR of crude reaction mixture showed the appearance of C=O at 1770cm^{-1}, consistent with stretching in the presence of an ortho electron-withdrawing substituent

26. Photolysis of N-allyl-N-benzoyl-O-2-nitrobenzylhydroxylamine.



Photolysis of N-allyl-N-benzoyl-O-benzylhydroxylamine was carried using a procedure similar to the photolysis of N-benzoyl--O-2-nitrobenzylhydroxylamine (expt. 25). Evaporation of solvent under reduced pressure produced a dark brown viscous oil. T.l.c. (SiO_2, ethyl acetate/pet.ether 60-80 60 : 40) showed a complex mixture, one component of which gave a positive test for hydroxamic acid with ferric chloride (purple colouration). Attempts of separation by preparative t.l.c. (SiO_2, $CHCl_3$/MeOH 9 : 1) proved unsuccessful.

27. Preparation of N-allyl-O-benzoylhydroxylamine hydrochloride.



A solution of freshly distilled allylamine (5.71 gms, 0.1 mole) in 10 cm^3 benzene (sodium dried) was added dropwise with stirring to a solution of freshly crystallized dibenzoyl peroxide (12.11 gms, 0.05 mole) in sodium dried benzene (50 cm^3). The reaction mixture was cooled on ice. After reaction was complete i.e. when cooled down, 50 cm^3 of diethyl ether was added. The mixture was shaken with water (3 x 100 cm^3). The organic phase was dried with anhydrous sodium sulphate and the hydrochloride then precipitated with dry HCl. The hydrochloride was filtered

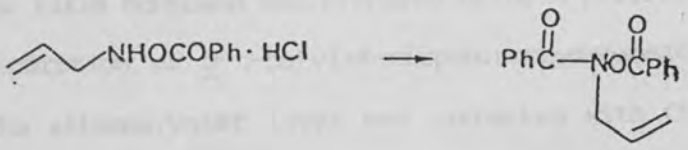
(crude yield, 1.76 gms, 16.5%). Recrystallization from ethanol gave a pure white powder (500 mg, 4.7%), mpt. 112-114°C.

IR (νcm^{-1}, nujol): 2722-2335 (v br. NH^+, NH_2^+ str.), 1757 s (C=O str. ester), 1600 w (C=C aromatic str.).

^{1}H-nmr (δ ppm, $CDCl_3$): 3.96-4.00 (d, 2H, -N-CH_2-), 5.30-5.50 (unresolved d, 2H, -N-CH_2-CH=CH_2), 5.60-6.00 (m, 1H, -N-CH_2-CH=CH_2), 6.60-7.00 (br.s, 1H, -NH-), 7.38-7.90 (m, 5H, Ar-H).

Elemental analysis: Found C, 56.19; H,5.65; N,6.7%. $C_{10}H_{12}NO_2Cl$ requires C, 56.2; H, 5.62; N, 6.56%.

28. Preparation of N-allyl-N-benzoyl-O-benzoylhydroxylamine.



The title compound was prepared using a procedure similar to the of N-t-butyl-O-4-nitrobenzoylbenzohydroxamic acid (expt. 2). Except that 2 moles equiv. of pyridine was used. The crude reaction product, an amber oil, was further purified by flash chromatography (SiO_2, ethyl acetate/pet. ether 60-80 20 : 80) to give N-allyl-N-benzoyl-O-benzoylhydroxylamine a pale amber oil which showed a single spot on t.l.c, (3.20 gms, 61% based upon hydrochloride).

IR (ν cm^{-1}, neat): 3064-3031 (CH aromatic str.), 2986-2850 (CH aliphatic str.), 1762 s (C=O ester str.), 1674 s (C=O amide

str.), 1601 (C=C aromatic str.).

^{1}H-nmr (δ ppm, $CDCl_3$): 4.30-4.47 (m or dd, 2H, -N-CH_2-), 5.05-5.30 (m, 2H, -N-CH_2-CH=CH_2), 5.84-6.00 (m, 1H, -N-CH_2-CH=CH_2), 7.10-7.95 (m, 10H, Ar-H).

Mass spectrum (m/z 70eV): M^+(281, 33%), 161(PhCO-NH-CH_2-CH=CH_2^+), 122 (base peak), 105 ($PhCO^+$, 99%).

Elemental analysis: Found C, 71.8; H, 5.08; N, 5.20%. $C_{17}H_{15}NO_3$ requires C, 71.3; H, 5.58; N, 5.20%.

29. Preparation of N-allylbenzohydroxamic acid.

The title compound was prepared using a procedure similar to the preparation of N-t-butyl-4-nitrobenzohydroxamic acid (expt. 3). The ethanol/water layer was extracted with $CHCl_3$ (3 x 100 cm^3), then the organic layer was dried over anhydrous sodium sulphate, filtered and solvent removed under reduced pressure. The reaction products were separated by flash chromatography (SiO_2, CH_2Cl_2/ethyl acetate 75 : 25) to give a crude yellow solid, (0.87 gms, 77%), mpt. 50-52^oC. Recrystallization from CCl_4/pet. ether 40-60 gave the hydroxamic acid as a white powder (420 mg, 37%), mpt. 54-56^oC.

IR (ν cm^{-1}, nujol): 3184 (br.s OH str.), 1606 s (C=O amide str.), 1596 (C=C aromatic str.).

^{1}H-nmr (δ ppm, $CDCl_3$): 4.10-4.40 (d, 2H, -N-$\underline{CH_2}$-), 5.10-5.50 (m or dd, 2H, -N-CH_2-CH=$\underline{CH_2}$), 5.55-6.45 (m, 1H, -N-CH_2-$\underline{CH}$=CH_2), 7.05-7.95 (m, 5H, Ar-H).

Mass spectrum (m/z, 70eV): M^+ (177), 176(M^+ - H), 161 (M^+ - O), 105 (base peak, $PhCO^+$).

30. Preparation of N-(1-adamantanecarbonyl)-N-allyl-O-benzoyl-hydroxylamine.

The title compound was prepared using a similar procedure to the preparation of O-benzoyl-N-t-butyl-4-nitrobenzohydroxamic acid (expt. 2). Recrystallization from CH_2Cl_2/pet. ether 40-60 gave the title compound, (1.48 gms, 93%), mpt. 80-82^oC.

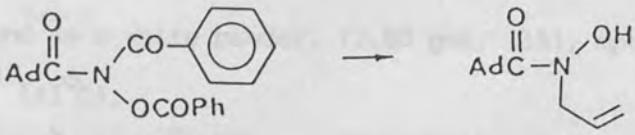
IR (νcm^{-1}, nujol): 1768 s (C=O ester str.), 1651 s (C=O amide str.), 1600 (C=C aromatic str.).

^{1}H-nmr (δ ppm, $CDCl_3$): 1.45-2.25 (two s, 15H, Ad hydrogens), 4.30-4.55 (d, 2H, -N-$\underline{CH_2}$-), 4.95-5.45 (dd, 2H, -N-CH_2-CH=$\underline{CH_2}$), 5.50-6.15 (m, 1H, -N-CH_2-$\underline{CH}$=CH_2), 7.25-8.25 (m, 5H, Ar-H).

Elemental analysis: Found C, 73.86; H, 7.52; N, 3.6% $C_{21}H_{25}NO_3$ requires C, 74.34; H, 7.38; 4.13%.

Mass spectrum (m/z 35eV): no M^+ present, 219 (AdCONH-CH_2-CH=CH_2^+, 4%), 163 ($AdCO^+$, 1.6%), 135 (base peak, Ad^+).

31. Preparation of N-(1-adamantanecarbonyl)-N-allylhydroxylamine.



The title compound was prepared using a procedure similar to the preparation of N-t-butyl-4-nitrobenzohydroxamic acid (expt. 3). Recrystallization from CH_2Cl_2/pet. ether 40-60 gave hydroxamic acid as a white crystalline solid, (0.49 gms, 48%), mpt. 103-105°C.

IR (νcm^{-1}, nujol): 3139 (br.s OH str.), 1586 (C=O amide str., lowest reported C=O str.).

^{1}H-nmr (δ ppm, $CDCl_3$): 1.60-2.20 (d, 15H, Ad-H), 4.20-4.45 (d, 2H, $-N-CH_2-$), 5.05-5.50 (dd, 2H, $-N-CH_2-CH=CH_2$), 5.60-6.20 (m, 1H, $-N-CH_2-CH=CH_2$).

Elemental analysis: Found C, 71.19; H, 8.93; N, 5.74% $C_{14}H_{21}NO_2$ requires C, 71.49; H, 8.93; N, 5.96%.

Mass spectrum (m/z 35eV): no M^+ present, 219 ($AdCONH-CH_2CH=CH_2^+$), 163 ($AdCO^+$), 135 (base peak, Ad^+).

32. Preparation of N-benzyl-O-benzoylhydroxylamine hydrochloride.

The title compound was prepared using similar procedure to

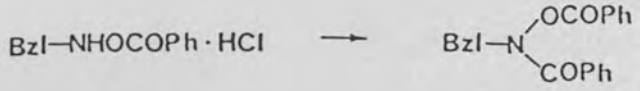
the preparation of N-allyl-O-benzoylhydroxylamine hydrochloride (expt. 27). Recrystallization from ethanol gave the title compound as a white powder, (2.80 gms, 11%), mpt. 135-137°C (lit. mpt.[79] 141°C).

IR (ν cm^{-1}, nujol): 1764 (C=O ester str.).

^{1}H-nmr : nmr could not be recorded due to in solubility in organic deutereo solvents and instability in D_2O.

Elemental analysis: Found C, 63.69; H, 5.57; N, 5.35% $C_{14}H_{14}NO_2Cl$ requires C, 63.71; H, 5.31; N, 5.31%.

33. Preparation of N-benzoyl-N-benzyl-O-benzoylhydroxylamine.



The title compound was prepared by a procedure similar to the preparation of N-allyl-N-benzoyl-O-benzoylhydroxylamine (expt. 28). Recrystallization from CCl_4 gave N-benzoyl-N-benzyl-O-benzoylhydroxylamine as a white crystalline solid, (1.30 gms, 40%), mpt. 86-88°C.

IR (ν cm^{-1}, nujol): 1762 (C=O ester str.), 1630 (C=O amide str.), 1598 (C=C aromatic str.).

^{1}H-nmr (δ ppm, $CDCl_3$): 5.05 (s, 2H, -N-CH_2-), 7.15-8.25 (m, 5H, Ar-H).

Elemental analysis: Found C, 76.50; H, 6.13; N, 4.02% $C_{21}H_{17}NO_3$ requires C, 76.13; H, 5.14; N, 4.25%.

34. Preparation of N-benzylbenzohydroxamic acid.

The title compound was prepared using a similar procedure to the preparation of N-allylbenzohydroxamic acid (expt. 29). Recrystallization from CH_2Cl_2/pet. ether 40-60 gave the title compound as a white crystalline solid, (0.400 gms, 55%), mpt. 98-100°C. (lit. mpt.[64] 99-101°C)

IR (ν cm^{-1}, nujol): 3268 (max. OH str.), 3062 (CH aromatic str.), 1627 (C=O amide str.).

^{1}H-nmr (δ ppm, $CDCl_3$): 4.80 (s, 2H, -N-CH_2-), 7.05-7.75 (m, 10H, Ar-H).

35. Preparation of N-n-propyl-O-benzoylhydroxylamine hydrochloride.

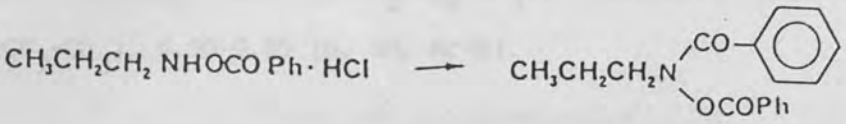
$$CH_3CH_2CH_2NH_2 \longrightarrow CH_3CH_2CH_2NHOCOPh \cdot HCl$$

The title compound was prepared using a similar procedure to the preparation of N-allyl-O-benzoylhydroxylamine hydrochloride (expt. 27). Recrystallization from ethanol gave the title compound as a white crystalline solid, (1.80 gms, 8.4%), mpt. 128-129°C (lit. mpt.[72] 129°C).

IR (νcm^{-1}, nujol): 3065-3034 (CH aromatic str.), 2967-2877 (CH aliphatic str.), 1767s (C=O ester str.), 1668 s (C=O amide str.), 1600 (C=C aromatic str.).

^{1}H-nmr (δ ppm, $CDCl_3$): 0.90-1.20 (t, 3H, $-N-CH_2-CH_2-\underline{CH_3}$), 1.45-2.10 (sextet, 2H, $-N-CH_2-\underline{CH_2}-CH_3$), 3.70-4.00 (t, 2H, $-N-\underline{CH_2}-CH_2-CH_3$), 7.05-8.25 (m, 10H, Ar-H).

36. Preparation of N-benzoyl-N-n-propyl-O-benzoylhydroxylamine.

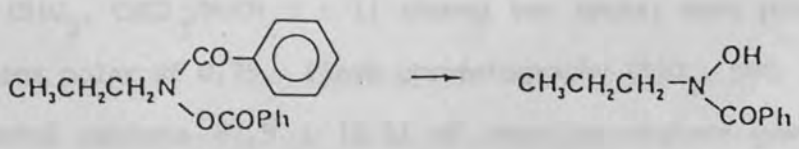


The title compound was prepared using a procedure similar to the preparation of N-allyl-N-benzoyl-O-benzoylhydroxylamine. Flash chromatography (SiO_2, ethyl acetate/pet. ether 40-60 40 : 60) of the reaction mixture gave N-benzoyl-N-n-propyl-O--benzoylhydroxylamine as a colourless viscous oil (1.10 gms, 97%).

IR (ν cm^{-1}, nujol): 3065-3034 (CH aromatic str.), 2967-2877 (CH aliphatic str.), 1767 s (C=O ester str.), 1668 s (C=O amide str.), 1600 (C=C aromatic str.).

^{1}H-nmr (δ ppm, $CDCl_3$): 0.90-1.20 (t, 3H, -N-CH2-CH-$\underline{CH_3}$), 1.45-2.10 (sextet, 2H, $-N-CH_2-\underline{CH_2}-CH_3$), 3.70-4.00 (t, 2H, $-N-\underline{CH_2}-CH_2-CH_3$), 7.05-8.25 (m, 10H, Ar-H).

37. Preparation of N-n-propylbenzohydroxamic acid.



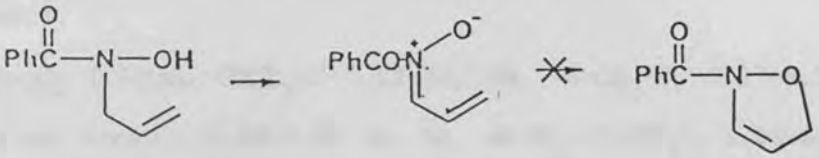
The title compound was prepared using a procedure similar to the preparation of N-allylbenzohydroxamic acid (ept. 29). Flash chromatography (SiO_2, pet. ether 60-80/ethyl acetate 80 : 20) of

crude product gave the hydroxamic acid as a white solid, (0.31 gms, 42%), mpt. 66-68°C (lit. mpt.[70] 66-69°C).

IR (ν cm^{-1}, nujol): 3192 (OH str.), 2964-2880 (CH aliphatic str.), 1614 s (C=O amide str.), 1575 (C=C str.).

^{1}H-nmr (δ ppm, $CDCl_3$): 0.85-1.10 (t, 3H, $-N-CH_2-CH_2-\underline{CH}_3$), 1.30-1.95 (sextet, 2H, $-N-CH_2-\underline{CH}_2-CH_3$), 3.40-3.70 (t, 2H, $-N-\underline{CH}_2-CH_2-CH_3$), 6.90-7.85 (m, 5H, Ar-H).

38. One-electron oxidation of N-allylbenzohydroxamic acid.



N-Allylbenzohydroxamic acid (103 mg, 0.58 mmole) was taken up in methylene chloride (50 cm^3) containing silver oxide (271 mg, 1.2 mmole) and anhydrous sodium sulphate (517 mg, 3.64 mmole). The solution was stirred at room temperature for 6 hours. The reaction showed, upon t.l.c. inspection, the complete disappearance of the starting material and the presence of two main components. The inorganic solids were removed from the reaction mixture by filtration through celite. Then the solvent was removed under reduced pressure to yield an amber oil (75 mg). T.l.c. (SiO_2, $CHCl_3$/MeOH 9 : 1) showed two spots; more polar Rf 0.65, less polar Rf 0.79. Flash chromatography (SiO_2, pet. ether 60-80/ethyl acetate 87.5 : 12.5) of reaction mixture gave two components.

More polar fraction (35.3 mg).

IR (ν cm^{-1}, neat): 3064 (CH aromatic str.), 2985-2920 (CH

aliphatic str.), 1763 s (C=O ester str.), 1662 s (C=O amide str.), 1601 (C=C aromatic str.).

^{1}H-nmr (δ ppm, $CDCl_3$): 4.30-4.47 (d, 2H, -N-C<u>H</u>$_2$-), 5.05-5.30 (m, 2H, -N-CH_2CH=C<u>H</u>$_2$), 5.84-6.00 (m, 1H, -N-CH_2C<u>H</u>=CH_2), 7.10-7.95 (m, 10H, Ar-H).

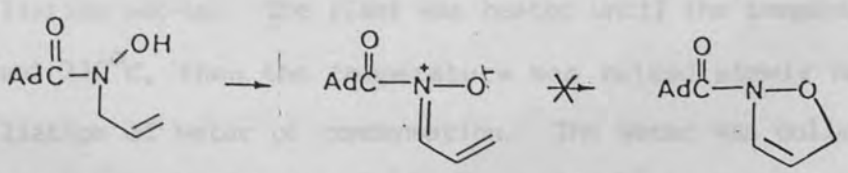
Less polar fraction (7.7 mg)

IR (ν cm^{-1}, neat): 3085 (CH aromatic str.), 2921-2852 (CH aliphatic str.), 1642 s (C=O amide str.), 1603 (C=C aromatic str.).

^{1}H-nmr (δ ppm, $CDCl_3$): 4.12 (s, 2H, -N-C<u>H</u>$_2$-), 5.17-5.32 (t, 2H, do not known), 5.89-5.97 (m, 1H, -N-CH_2-C<u>H</u>=CH_2), 6.00-6.20 (br.s, 1H, -N<u>H</u>-)

Structure shows PhCONHCH_2CH=CH_2 although spectral assignment is not conclusive.

39. One-electron oxidation of N-(1-adamantanecarbonyl)-N-allyl-hydroxylamine.



Oxidation of title compound was carried out using a similar procedure to the oxidation of N-allylbenzohydroxamic acid (expt. 38). The reaction mixture showed, upon t.l.c. (SiO_2, ethyl acetate/pet. ether 40-60 25 : 75) inspection, the presence of two main components. ^{1}H-N.m.r. shows one main component, with no

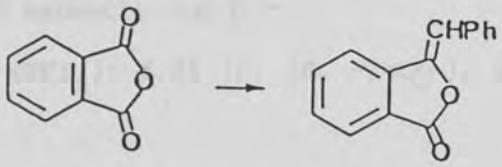
presence of ring compound. The main component is most likely AdCON(allyl)-OCOAd.

IR (ν cm^{-1}, neat): 2958-2927 (CH aliphatic str.), 1720 s (C=O ester str.), 1644 s (C=O amide str.).

^{1}H-nmr (δppm, $CDCl_3$): 1.80-2.10 (two s, 30H, 2 Ad-H), 4.25-4.35 (d, 2H, $-N-CH_2-$), 5.30 (undefined d, 2H, $-N-CH_2-CH=CH_2$), 5.0-6.10 (m, 1H, $-N-CH_2CH=CH_2$).

Time did not permit the purification of the compound to allow elemental analysis and mass spectrum analysis.

40. Preparation of benzalphthalide.



The title compound was prepared according to the method by R. Weiss.[160]

Phthalic anhydride (sublimed, 65 gms, 0.44 mole), phenylacetic acid (71 gms, 0.52 mole) and sodium acetate (1.69 gms, 0.22 mole) was placed in the flask of the normal distillation set-up. The flask was heated until the temperature reached 230°C, then the temperature was raised slowly until distillation of water of condensation. The water was collected in a small vessel and its quantity noted from time to time in order to monitor progress of the reaction. The operation was conducted so that the temperature rose from 230°C to 240°C over 2 hours. The mixture was then maintained at 240°C until the distillation of water ceased (this required about one additional

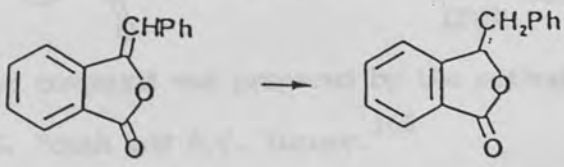
hour). A brown residue resulted. A test portion was treated with a little ethanol followed by boiling (when reaction is complete the material dissolves readily).

When reaction was complete the reaction mixture was cooled to 90-95°C, and dissolved in absolute ethanol (400 cm^3). The solution was then filtered from the inorganic residue and allowed to cool when yellow crystals of crude benzalphthalide separated, mpt. 87-91°C, (95.05 gms, 43%). Recrystallization from ethanol gave pure material (88.80 gms, 40%), mpt. 99-100°C (lit. mpt.[160] 100-101°C).

IR (ν cm^{-1}, nujol): 1774 s (C=O ester str.), 1657 s (conj. C=C str.), 1606 (C=C aromatic str.).

^{1}H-nmr (δ ppm, $CDCl_3$): 6.05 (s, 1H, -C=CH-), 6.80-7.75 (m, 9H, Ar-H).

41. Preparation of 3-benzylphthalide.



The title compound was prepared by the method of W. Treib et al.[161]

A mixture of potassium hydroxide (11.25 gms, 0.20 mole) and benzalphthalide (30.00 gms, 0.135 mole) was dissolved in water (66 cm^3), followed by a further addition of KOH (7.5 gms, 0.134 mole). The solution was heated to boiling and zinc powder (9.38 gms, 0.144 mole) was then added with stirring. After the

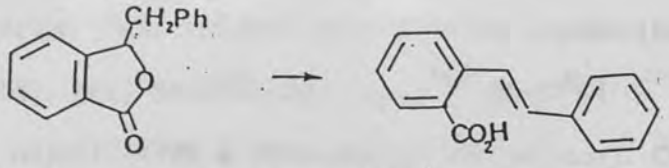
solution had lost its colour it was filtered to remove residual Zn dust and the crude title compound, a green/white oily solid (+ trapped water), (32.01 gms, 112%) was precipitated with HCl. Recrystallization using propan-2-ol (a slight excess was required to allow slow crystallization) gave a white crystalline solid, 23.82 gms, 79%), mpt. 57-59°C (no lit. mpt. recorded).

NB. the Zn reaction was monitored by the removal of red colour from solution to an end-point orange/red colouration.

IR (ν cm^{-1}, nujol): 1751 s (C=O lactone str.), 1599 (C=C aromatic str.).

^{1}H-nmr (δppm, $CDCl_3$): 2.90-3.30 (d, 2H, $-CH_2-Ph$), 5.30-5.70 (t, 1H, $-CH-CH_2-Ph$), 6.70-8.00 (m, 9H, Ar-H).

42. Preparation of trans-stilbene-2-carboxylic acid.



The title compound was prepared by the method of W. Treib et al[161] and G.G. Booth and A.F. Turner.[162]

A solution of 3-benzylphthalide (20 gms, 0.089 moles) in water (31.3 cm^3) and ethanol (31.3 cm^3) was taken to dryness by distillation under normal atmospheric pressure. The residue was then held at 100°C/15 mmHg for one hour, then the temperature raised to 200°C/15 mmHg for 4 hours. The crude title compound, an orange/yellow solid, (20.31 gms, 102%), mpt. 148-155°C was recovered by acidification of an aqueous solution of the residue using conc. HCl. Recrystallization from CCl_4/trace of

propan-2-ol gave white powder, (13.93 gms, 70%), mpt. 155-157°C (lit. mpt.[162] 160-162°C).

IR (ν cm^{-1}, nujol): 3385 s (br.s OH str.), 1677 (C=O aryl str.), 1628 m (conjugated C=C str.).

^{1}H-nmr (δ ppm, $CDCl_3$): 6.75-7.05 (d, 1H, -C=CH-Ph), 7.05-8.10 (m, 10H, Ar-H and HCO_2-Ar-CH=CH-), 8.30-9.00 (br.s, 1H, $-CO_2H$).

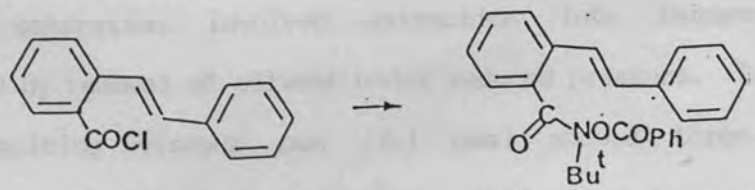
43. Preparation of trans-stilbene-2-carboxylic acid chloride.

The title compound was prepared using a similar procedure to the preparation of 1-adamantanecarboxylic acid chloride (expt. 4), except that the reaction time was 32 hours. Recrystallization from toluene gave a white crystalline solid, (1.15 gms, 95%), mpt. 55-57°C (lit. mpt.[163] 56-57°C)

IR (ν cm^{-1}, nujol): 1775 s (C=O str.), 1631 m (conj. C=C str.), 1597 (C=C aromatic str.).

^{1}H-nmr (δ ppm, $CDCl_3$): 7.43-7.55 (d, 1H, J=16Hz, -C=CH-Ph), 7.65-8.25 (m,10H,Ar-H and Ar-CH=CH-Ph).

44. Preparation of N-(trans-stilbene-2-carbonyl)-N-t-butyl-O-benzoylhydroxylamine.



The title compound was prepared using a procedure

similar to the preparation of N-t-butyl-O-benzoyl-4-nitrobenzohydroxamic acid (expt. 2). Recrystallization from CH_2Cl_2/pet. ether 60-80 gave N-(trans-stilbene-2-carbonyl)-N-t-butyl-O-benzoylhydroxylamine as a white solid (1.70 gms, 64%), mpt. 139-141°C.

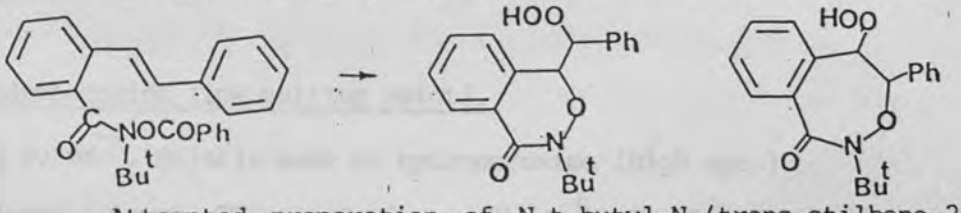
IR (ν cm^{-1}, nujol): 1763 s (C=O ester str.), 1668 s (C=O amide str. shoulder on carbonyl peak due to conjugated C=C str.), 1598 m (C=C aromatic str.).

^{1}H-nmr (δ ppm, $CDCl_3$): 1.65 (s, 9H, Bu^t), 7.00-7.80 (m, 16H, Ar-H and Ph-H).

Mass spectrum (m/z, 35eV): 399 (M^+, 9.3%), 221 ($Ar-CO-N^+$), 207 (base peak, $ArCO^+$), 57 (M^+ - 342, Bu^t).

Elemental analysis: Found C, 78.20; H, 6.42; N, 3.41%. $C_{26}H_{25}NO_3$ requires C, 78.20; H, 6.25; N, 3.51%.

45. Hydrolysis of N-t-butyl-N-(trans-stilbene-2-carbonyl)-O-benzoylhydroxylamine by hydrazine hydrate in the presence of air.



Attempted preparation of N-t-butyl-N-(trans-stilbene-2-carbonyl)hydroxylamine employed a similar procedure to the preparation of N-t-butyl-4-nitrobenzohydroxamic acid (expt. 3). Except separation involved extraction into benzene/ether, followed by removal of solvent under reduced pressure. T.l.c. of the resulting viscous gum (2.1 gms) showed three spots. Separation by flash chromatography (SiO_2, ethyl acetate/pet.

ether 60-80 40 : 60) gave as second fraction (0.5 gms) a colourless gum which, on prolonged treatment with $CHCl_3$/pentane gave a solid hydroperoxide (105 or 106), mpt. 138-140°C. concentration of the mother liquor gave a second crop of lower melting material (105 or 106) (mpt. 121°C).

Hydroperoxide (high melting point).

IR (ν cm^{-1}, nujol): 3212 (OO-H str.), 1650 s (C=O amide str.), 1603 (C=C aromatic str.).

^{1}H-nmr (δ ppm, $CDCl_3$): 1.65 (s, 9H, Bu^t), 5.34 (s, 2H, -CH-CH-), 7.00-8.00 (m, 9H, Ar-H), 8.33 (br. s, 1H, OOH).

Elemental analysis : found C, 69.74; H, 6.47; N, 4.19%. $C_{19}H_{21}NO_4$ requires C, 69.74; H, 6.42; N, 4.28%.

Mass spectrum (m/z, CI-isobutane): no M^+ peak, 313 (M^+ - H, 1%), 311 (Ar-OH^+, 3.8%), 310 (Ar-O^+, 15%), 254 (6.39%), 204 (base peak, 100%).

Mass spectrum interpretation was tentative.

Hydroperoxide (low melting point).

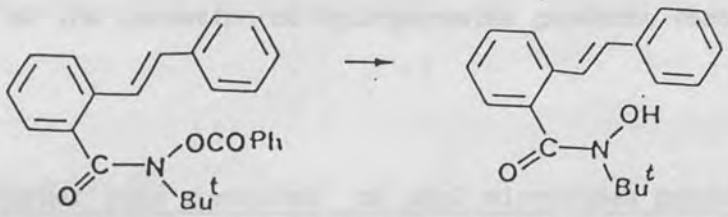
IR (ν cm^{-1}, nujol): same as hydroperoxide (high mpt.).

1H-nmr (δ ppm, $CDCl_3$): 1.65 (s, 9H, Bu^t), 5.10-5.60 (quartet or dd, 2H, -CH-CH-), 7.00-8.00 (m, 9H, Stilbene-H), 8.33 (br.s, 1H, OOH).

Elemental analysis: Found C, 69.65; H, 6.48; N, 4.16%. $C_{19}H_{21}NO_4$ requires C, 69.74; H, 6.42; N, 4.28%.

Mass spectrum (m/z, CI-isobutane): same as hydroperoxide (high mpt.).

46. Preparation of N-t-butyl-N(trans-stilbene-2-carbonylhydroxylamine.



N-t-Butyl-N(trans-stilbene-2-carbonyl)-O-benzoylhydroxylamine (3.75 gms, 9.40 mmole) was added to a solution of sodium methoxide (4.28 gms, 0.080 mole) in MeOH (25% solution) in 90 cm^3 absolute ethanol taking care to degass the solution continuously with argon and keeping the reaction temperature below 10^oC (with ice/water bath). After stirring for 1 1/2 hours, the reaction was extracted with ether (dried and degassed) (3 x 50 cm^3). The portions were combined and solvent removed under reduced pressure to give a pale yellow oil. Recrystallization from CCl_4/pentane under argon gave the titled hydroxamic acid (0.70 gms, 24%), mpt. 63-68^oC. The product was kept under vacuum in a desiccator. The product undergoes oxygenation in solvents and also in solid form, therefore must be kept in argon atmosphere after drying.

IR (ν cm-1, nujol): i.r. could not be recorded since compound under went oxidation in operation time.

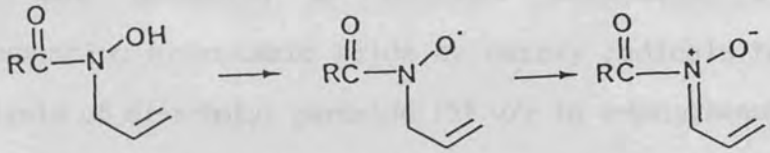
Elemental analysis can not be done due to oxidation to hydroperoxide.

^{1}H-nmr (δ ppm, $CDCl_3$): 1.29 (s, 9H, Bu^t), 7.00-7.65 (m, 11H, stilbene-H), 8.25 (br. s, 1H, N-OH).

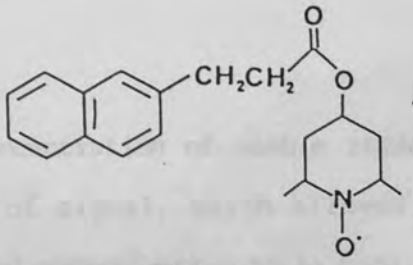
The ^{1}H-n.m.r. of the title hydroxamic acid left in $CDCl_3$ in the presence of air for 2 days showed the appearance of a singlet

at δ (5.34 ppm) and a quartet at δ (5.10-5.60 ppm). This was indicative of the formation of hydroperoxide products (see expt. 45).

47. Second-order rate constants of acyl nitroxides produced by the photolytic hydrogen abstraction of N-primary alkylhydroxamic acids.



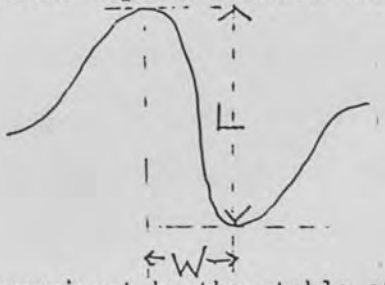
E.s.r. can be used to follow the generation or disappearance of radicals during a reaction by following the intensity of the e.s.r. signal. At a given frequency and constant applied magnetic field, the intensity of the energy absorbed in resonance is proportional to the concentration of radical species. In order to determine the proportionality constant and obtain the exact concentration, a comparison with a separate standard radical sample was made. The stable crystalline nitroxide 4-(β-naphthyl-propionyl)-2,6-tetramethylpiperidinyloxy was used for this purpose.



The procedure was as follows - the recording of the 1st derivative of 1.84 10^{-5} M standard radical in t-butylbenzene in a

glass e.s.r. tube was made, followed by cleaning with concentrated HCl, then distilled water, and then benzene. The same e.s.r. tube (i.e. same Q value) was then used for the kinetic study keeping all e.s.r. settings unchanged apart from spectrometer gain; the 1^{st} derivative of the spectrum of the acyl nitroxide under study was recorded on the scale on the same e.s.r. chart paper as the standard. The nitroxides for kinetic study were generated by hydrogen abstraction from the corresponding hydroxamic acids by butoxy radicals formed by photolysis of di-t-butyl peroxide (5% v/v in t-butylbenzene).

The spectra of the acyl nitroxides were monitored at very high modulation amplitude (1.25×10^{-1} - 2.0×10^{-1}) (over modulation), this removed all fine detail of three line spectra into single Lorenzian lines, where area of peak = LW^2. The concentration of each acyl nitroxide was calibrated at the



beginning of each experiment by the stable standard radical.

Calibration

The known concentration of stable radical was calibrated against intensity of signal, which allowed the relationship between intensity and concentration to be made for radicals under study. Due to the impracticability of making the standard

radical in inert t-butylbenzene with concentrations as low as 10^{-6}-10^{-7} M (a common radical concentration); the linear relationship between receiver gain and the intensity of signal of and the stable radical was used. The adjustment of receiver gain (keeping all other parameters constant) for the spectrum of unknown concentration of acyl nitroxide allowed the spectrum to be on the same scale on e.s.r chart recorder as standard. Therefore the linear relationship between concentration at different receiver gain allowed the calculation of unknown acyl nitroxide radical concentrations.

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